

**OPTIMIZATION AND ACCEPTANCE OF
ENTERIC MRI IN INFLAMMATORY BOWEL
DISEASE**

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DECLARATION

I Rehana Hafeez confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Inflammatory bowel disease is a chronic inflammatory condition of bowel. CT and barium fluoroscopy are main stay of radiological investigation but impart high radiation dose. MRI is a safe and less invasive technique to assess bowel. The thesis examines the use of magnetic resonance Imaging in enteric inflammatory bowel disease.

A discussion on inflammatory bowel disease and overview of MRI techniques, diagnostic features and review of literature is described.

A national survey about the uptake of MRI for the investigation of IBD showed that 38% of radiology departments offered enteric MRI and barium studies remaining the main imaging investigation performed. A proforma administered to clinicians in OPD showed significant increase in their diagnostic confidence for small bowel disease after MRE, which had positive impact on therapeutic strategy of 61% of patients.

The results of a prospective studies investigating MR colonography as a biomarker of disease activity are then presented. Quantitative measurements of contrast enhancement in normal colon have shown intersegmental differences. Three proposed qualitative MRI scores of disease activity correlated with endoscopic disease activity, but correlation with histopathological scores was less apparent.

The use of unprepared colonic MRI in assessment of acute colitis is then investigated. A qualitative total colonic inflammation score (TCIS) proposed and validated against clinical standards including stool frequency and CRP. It also has prognostic ability for length of hospital stay. Region of interest derived quantitative measurements from the

colon wall including T2 signal and contrast enhancement are then compared to a validated clinical score of colitis activity. Quantitative markers seemed less robust than qualitative scores, although quantified contrast enhancement is correlated with disease severity.

Patient experiences of MR Colonography and colonoscopy are investigated by using face-to-face qualitative interviews, together with a quantitative questionnaire. Patient preference is highly complex but patients expressed overall preference for MRC.

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Glossary

IBD – Inflammatory bowel disease

CDAI - Crohn's disease activity index

CC – Colonoscopy

CDEIS - Crohn's disease endoscopic index of severity

SES- CD – Endoscopic Crohn's disease index

BaFT – Barium follow through

DCBE – Double contrast barium enema

CTE – CT Enterography

CTC – CT Colonography

MRE – MR Enterography

MRC – MR Colonography

HASTE – Half Fourier acquisition single shot turbo spin echo

FLASH – Fast Low Angle Shot

FISP – Fast imaging with steady state precision

VIBE – Volumetric interpolated breath hold examination

EPI-DWI – Echo planar diffusion weighted images

ADC – Apparent Diffusion Coefficient

TCIS – Total colonic inflammatory score

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Ethical Approval and Patient Recruitment

Ethical permission was obtained for all the studies from Ethical committee, University College London and good medical practice guidelines followed. (07/H0714/82 and 07/H0715/71)

Patients were recruited in four main categories for these studies.

Comparative studies with colonoscopy and assessment of patient experience

Inflammatory Bowel Disease (IBD) patients

In order to develop MRI parameter values in patients with IBD, patients undergoing endoscopy for IBD related indications were recruited after identification in the following ways

- a. Via review of the clinical referral letter to the department of endoscopy
- b. Via outpatient IBD clinic/inpatient ward. An information sheet, consent form and an invitation letter were given to all of these patients.

Eligible patients selected from endoscopy unit were sent the patient information sheet and consent form by post accompanied by a letter inviting them to take part in the study.

Non-IBD patients

Patients undergoing routine outpatient colonoscopy for non-IBD related indications were recruited for the study. They were identified via review of the clinical referral letter to the department of endoscopy and were selected such that their age distribution was similar to that of the IBD patients. An invitation letter along with patient information sheet and consent forms were sent to them by post. The letter was sent at least 3 weeks prior to the date of their colonoscopy to give time for them to consider participation.

Patients from these two groups had undergone the standard bowel preparation for the planned colonoscopy before attending the hospital on that day. MRI was performed before colonoscopy (CC) and signed informed consent was obtained for all.

Patients with acute colitis

Given the clinical severity of acute colitis, all eligible patients were inpatients at UCLH

Patients were identified in three ways

- a. At the weekly GI luminal MDT attended by gastroenterologists, colorectal surgeons and radiologists. All patients with colitis were discussed at this meeting.
- b. Via direct referral by gastroenterologists or surgeons looking after the patients

- c. Via referrals to the department of Imaging for appropriate radiological investigation of patients with severe colitis including plain films, CT, MRI or ultrasound

Eligible patients were given the patient information sheet and consent form, accompanied by a letter inviting them to take part in the study. For those patients agreeing to take part, signed informed consent before the MRI.

Diagnostic impact study

An ethical waiver for the study was obtained from the UCLH ethics committee. New or follow up patients attending gastroenterology clinic between July 2008 till September 2009 referred for a small bowel MRI were included in this study.

Dedication

This thesis is dedicated to the memory of my parents and my brother Asif.

And to

My sisters – Their support have made it all possible

1 SECTION ONE

1.1 INTRODUCTION, HYPOTHESIS, AIMS AND STRATEGY

1.1.1 INTRODUCTION

Idiopathic inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis) are a chronic inflammatory condition of the bowel, predominately affecting the young and requiring lifelong medical and often surgical therapy (1). The natural history of the diseases is one of intermittent acute exacerbations characterised by an acute inflammatory response, separated by periods of relative quiescence. Medical therapy is based largely on immunosuppressive medication. Although relatively effective, these drugs are not without significant side effects, some of them life threatening, notably sepsis secondary to immunosuppression. Furthermore therapeutic agents such as anti-TNF are expensive and often require intravenous administration. Rational use of immunosuppressive therapies in IBD disease therefore relies on accurate identification of those patients with acute inflammation –so called “active disease”, who are most likely to respond to the treatment, together with assessment of the disease extent. The management of IBD and assessment of response to medication largely depends on accurately documenting the location, extent and the severity of the inflammation (2, 3). Unfortunately there is no single reliable non-invasive method to identify such patients. Clinical assessments based on patient symptomatology (such as the Crohn's disease activity index) are relatively subjective (4), and patients with inactive disease (such as those with chronic fibrotic strictures) often attract high scores. Biochemical markers

such as ESR and CRP are useful adjuncts (5) but again do not in themselves always differentiate reliably between active and chronic disease. Radiological investigations such as barium fluoroscopy provide useful information about the small bowel, but give little information about disease in the colon, and involve relatively high doses of radiation(6), which is problematic for young patients with chronic disease. Furthermore, they provide little information regarding extramural manifestations such as abscess formation, which can be of great importance in patients being considered for strong immunosuppression.

For those patients with colonic disease, conventional endoscopic techniques allow direct visual inspection of the mucosa. Endoscopy is an essential tool for diagnosis, management and prognostic evaluation of inflammatory bowel disease (7). The endoscopic appearances correlating with disease activity are well described and include aphthoid ulcerations, fissuring ulcers, cobblestoning and stenosis (8).

Colonoscopy has a prognostic role during a severe flare of disease both in ulcerative colitis and in Crohn's disease; moreover in Crohn's disease the evaluation of recurrent disease at anastomosis after surgical resection is a common indication.

Diagnostic endoscopy is considered a safe procedure but is invasive, often uncomfortable and patients are often reluctant to undergo the necessary repeat procedures over the course of their disease. Although the incidence of perforation after endoscopic procedures of the colon is low, it is very well recognized (9). Furthermore in those with colonic stricturing disease, complete colonoscopy may be impossible.

Radiological assessment of colonic IBD can be performed using both barium enema and CT Colonography. Both techniques expose patients to ionizing radiation. Although

barium enema facilitates assessment of relatively early mucosal disease, CT Colonography provides information on both mural and extra mural disease. (10, 11).

Magnetic resonance imaging has been advocated as a potentially useful investigation for assessment of those with IBD without exposing patients to ionising radiation (12-14). It images the whole bowel, providing simultaneous information about mural and extramural complications. Furthermore it has also been suggested that specific enteric and mesenteric appearances on MRI (such as bowel wall signal and contrast enhancement, lymphadenopathy, mesenteric high signal) are related directly to disease activity (15, 16) and as such may help rationalise the use of, and monitor response to immunosuppressive therapy.

The thesis examines the use of magnetic resonance Imaging (MRI) in enteric inflammatory bowel disease (IBD). The level of dissemination of MRI techniques in evaluating enteric IBD in the NHS is investigated via a national survey of radiologists and gastroenterologists. The impact of MRI Enterography is then studied using specifically designed diagnostic and therapeutic impact proformas applied to clinicians treating IBD. The thesis then focuses on the colon. The use of unprepared MRI in evaluating patients with acute severe colitis is investigated and a qualitative and quantitative MRI scoring system of severity proposed and tested against current clinical indices and patient outcome. The post contrast perfusion kinetics of the normal colon during MRColonography (MRC) is defined. The ability of MR Colonography to assess disease activity in the colon against an endoscopic and histological standard of reference is then addressed using qualitative MRI scoring systems. Patient experience of MRC is investigated by qualitative interviews, and a quantitative questionnaire applied comparing experiences during MRC and colonoscopy (CC).

1.1.2 HYPOTHESIS AND AIMS

1. European guidelines increasingly advocate the use of cross sectional techniques (MRI and SbUS) but dissemination in UK is patchy and adhoc.

Aim: to assess via postal survey, current utilization of small bowel imaging investigations for Crohn's disease within NHS radiological practice, and to gauge current gastroenterological referral patterns

2. MREnterography (MRE) has a positive diagnostic impact in patients under investigation for small bowel Crohn's disease and influences therapeutic strategy

Aim: to assess the impact of MRE on clinician diagnostic confidence and therapeutic strategy in patients with small bowel Crohn's disease

3. Abnormal contrast enhancement on MRI is advocated as a biomarker for inflammation in colitis, although the enhancement kinetics of normal colon are poorly described which can influence the interpretation of diseased colon on MRI.

Aim: to quantitatively assess mural enhancement in endoscopically proven normal colon and test for inter segmental differences

4. Mural characteristics on MR Colonography can be used as a biomarker of disease activity in IBD

Aim: to compare qualitative MRI scores of colonic disease activity against reference endoscopic and histological scores.

5. MRI and extramural characteristics on unprepared MRI can act as a biomarkers of disease active in acute colitis, and may predict ultimate outcome

Aim: To derive and validate a total colonic inflammatory score for assessing severity therapeutic response and prognosis in acute colitis.

6. Quantitative measurements of the bowel wall characteristics in acute colitis change in response to medical therapy and mirror objective measurements of clinical response.

Aim: to establish if quantitative MRI mural characteristics changes in response to therapeutic intervention and correlate with clinical markers of therapeutic response.

7. Currently available quantitative questionnaires regarding patient experience of MRC and CC are limited by the assumptions implicit in questionnaire design, and may not illicit true patient experience.

Aim: to apply qualitative techniques to assimilate data on patient experience and attitudes during MR Colonography and Colonoscopy and to evaluate how this is moderated by clinical indication

8. MRColonography (MRC) is better tolerated by patients, as a less invasive and more acceptable alternative to conventional colonoscopy (CC).

Aim: to evaluate patient experience of MR Colonography in comparison to conventional endoscopy using established questionnaires

1.1.3 THESIS STRATEGY

The thesis has five sections.

The first section consists of discussion about epidemiology and pathogenesis of inflammatory bowel disease and describes different treatment approaches. . It describes the available methods of diagnosis and disease assessment including clinical scores, biochemical indices and diagnostic modalities such as colonoscopy, barium enema, CT Colonography and MRI and describes the lack of an ideal method for defining the diagnosis and prognosis of IBD

This section also gives an overview of use of MRI for diagnosis and assessment of IBD including both MR Enterography and MR Colonography detailing technical aspects, diagnostic features and associated diagnostic pitfalls. The chapter includes a review of current literature and speculates on the future role of the modality.

In second section, the first chapter considers uptake of MRI in the NHS and its impact in the management of IBD patients. The findings of a national survey documenting current dissemination of MRI are presented.

The second chapter describes the design of a new diagnostic and therapeutic impact proforma to assess the influence of imaging tests in IBD management, and its prospective use with regard to MREnterography presented.

The third section focuses on developing MRI for assessing colonic IBD and consists of four studies.

The first study describes the quantitative MRI mural changes that occur following intravenous gadolinium administration in endoscopically normal colon and details inter-segmental differences.

The second study presents the results of a prospective study investigating MR Colonography as a potential biomarker of disease activity in colonic IBD. Three qualitative scoring systems of mural and extra mural tissue characteristics are tested against an endoscopic and histological standard of reference.

The third study investigates unprepared MRI in the assessment of acute severe colitis. In particular a qualitative total colonic inflammation score (TCIS) is developed and initially validated against clinical and biochemical standards of reference.

The fourth study describes the potential of quantitative bowel wall measurements on unprepared MRI in acute severe colitis to act as biomarkers of disease severity in comparison to an established combined clinical score of severity.

The fourth section reports a prospective study investigating patient experiences of MR Colonography and colonoscopy using face-to-face qualitative interviews, together with a quantitative questionnaire based around the 3 principal components of worry, physical experience and satisfaction.

The final section concludes this thesis with a discussion of the main findings and the implications for the dissemination of MR Colonography into day-to-day practice.

1.2 INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is usually categorized into Ulcerative colitis (UC) and Crohn's disease (CD). Although IBD occurs worldwide there is a noticeably higher incidence observed in the Westernized or industrialized areas of world. IBD is mainly a disease of young people with peak incidence between the ages of 10 -40 years, although 15 % cases are diagnosed after the age of 60. An incidence rate of 3.1 to 14.6/100,000 is seen in North America, whilst in the UK around 240,000 people are affected with IBD. The incidence of UC is approximately 10-20 per 100,000 per year and CD is 5-10 per 100,000 per year (1, 17-19).

UC and CD show significant differences in presenting symptoms, disease distribution, therapeutic strategy and prognosis. Crohn's disease commonly affects terminal ileum and proximal colon although it can involve whole of gastrointestinal tract. Bowel involvement is segmental typically manifesting as "skip lesions" where as UC usually affects rectum first (ulcerative proctitis) and in severe form can affect whole of colon as pan colitis. The features of Crohn's disease (CD) differ between the early and chronic stages of the disease. Typically in the early stage of CD there are areas of focal inflammation with aphthoid ulcerations and lymphoid hyperplasia. These progress to longitudinal and transverse mucosal ulcerations and eventually the ulceration may become transmural. Thereafter complications may arise including strictures, sinuses, fistulae and perienteric abscesses. Histologically, the chronic inflammatory process is typified by non- caseating granuloma formation. In the chronic stage of CD, there is fatty infiltration of bowel wall and fibrofatty infiltration of mesenteric fat. When disease becomes chronic it is characterized by fibrosis and stricture formation.

Conversely UC is a mucosal inflammatory process typified by ulceration of affected bowel. The disease characteristically begins in rectum and extends proximally to involve a variable parts of, or indeed the colon (11) (Table 1).

Ulcerative colitis	Crohn's Disease
Rectum \pm colon	Mouth to anus
Continuous	Discontinuous
Mucosal Disease	Trans mucosal disease (fissure, abscess, fistulae)
Muscular thickening	Fibrosis (stenosis)
Mucin depletion	Lymphoid ulcers, aggregates
Glandular damage	Granuloma
Colonic bleeding typical	Bleeding variable
Increase risk with smoking	Decrease risk with smoking

Table 1: Comparative features of UC and CD

Due to overlapping features, around 5 % of patients with IBD affecting the colon cannot be confidently classified as UC or CD even after considering all clinical, radiological, endoscopic and pathological information. Such patients are classified as indeterminate colitis (IC), although strictly speaking this is a post colectomy histological diagnosis

IBD not only involves the GI; extraintestinal manifestation are seen in 40% of the patients (20) (21) (Table 2).

Musculoskeletal	Arthritis, ankylosing spondylitis& sacroiliitis
Skin and mucous membranes	Oral ulcers, erythema nodosum, pyoderma gangrenosum, cutaneous vasculitis
Ocular	Conjunctivitis, Crohn's keratopathy
Hepatic	Primary sclerosing cholangitis
Cardiac	Endocarditis, myocarditis
Neurologic	Peripheral neuropathy
Bronchopulmonary	Sarcoidosis, fibrosing alveolitis

Table 2: Extra intestinal manifestations of IBD

1.2.1 PATHOGENESIS OF IBD

The pathogenesis of IBD is still not clear; genetic, environmental and immunological factors have all been considered. Epidemiological data confirms the familial nature of the disease, although suggested “triggers” include, environmental factors such as diet, smoking, non-steroidal anti-inflammatory drugs (NSAIDs) and infections. One fourth of IBD patients have an affected family member. Indeed UC and CD can occur in same family and share some features in genetic susceptibility. Many epidemiologic, immunologic and pathogenic features are common to both disorders, although genetic

factors are likely more important in CD. Environmental factors may have opposing effects on the two diseases. For example smoking worsens CD, but it decreases the risk of UC.

Epidemiological studies have considered diet, drug and vaccination history, seasonal variation, water supply and social circumstances. Extensive research has been performed investigating the role of luminal bacteria, biofilms, epithelial barrier functions and immune/ epithelial interactions as well as inflammatory process such as cell signaling pathways, cytokine profiles, lymphocyte trafficking, cell surface molecules and neuroimmune communications (22). Numerous bacteria and virus have been proposed as intimately associated with CD and UC including the measles virus, mycobacterium paratuberculosis diplostreptococcus and E coli, but as yet an infective etiology has not been established with any certainty.

1.2.2 TREATMENT OF IBD

UC may be severe and despite of new medical and surgical treatment, it still has excess mortality in the first two years of diagnosis. About 50 % of patient have a relapse in any year, which can be life threatening and of those with pancolitis around 20- 30% -will need total colectomy and ileal pouch formation. Conversely at least 50% of patients with CD will require surgery within the first 10 years of diagnosis and 70-80% within their lifetime due to failure of medical therapy or disease complications.

Medical therapy for IBD is rapidly evolving with new biological agents entering routine clinical practice, although therapeutic efficacy must be weighed against their side effect profile (Table 3).

1.2.2.1 Amino salicylates

This group includes mesalazine/ 5 ASA, Asacol and Pentasa. The drug class acts on epithelial cells by variety of mechanisms to moderate the release of lipid mediators, cytokines and reactive oxygen species. Side effects occur in 10 -45% of patients, most commonly headache, nausea, epigastric pain and diarrhea but serious idiosyncratic reactions including Steven Johnson syndrome, pancreatitis, agranulocytosis or alveolitis can occur. Patients need regular monitoring of renal functions while on therapy (2, 23, 24).

1.2.2.2 Corticosteroids

Corticosteroids are potent anti- inflammatory agents for moderate to severe relapses of both UC and CD. They inhibit of several inflammatory pathways such as suppressing interleukin transcription and arachidonic acid metabolism and stimulate of lymphocytes within the lamina propria of the gut. Early side effects are cosmetic (acne, moon face, edema), sleep and mood disturbance, dyspepsia and glucose intolerance while longer use is associated with osteoporosis, osteonecrosis of femoral head, myopathy and susceptibility to infections. Complete steroid withdrawal is facilitated by early introduction of azathioprine, adjuvant nutritional therapy or early surgery (25).

1.2.2.3 Thiopurines

Thiopurines are effective during active disease relapse and are commonly used to maintain remission in CD and UC. They are also used as steroid sparing agents and for postoperative prophylaxis of complex or fistulating CD. Leucopenia due to myelotoxicity can develop suddenly and unpredictably in between blood tests and hepatotoxicity and pancreatitis are well described. There is evidence for an associated small (<5%) increased in malignancy.

1.2.2.4 Methotrexate

Methotrexate use is second line in active or relapsing disease refractory to AZA and requires regular blood count and liver function tests. Early cytotoxicity is primarily gastrointestinal causing nausea, vomiting, diarrhea and stomatitis. In 10-18% of patients treatment has to be discontinued due to hepatotoxicity or pneumonitis (26, 27).

1.2.2.5 Cyclosporine

Cyclosporine prevents clonal expansion of T-cell subsets and its rapid onset of action, which makes it effective in management of severe UC. Use however cannot usually continue for more than 3-6 months because of toxicity. Major side effects include renal impairment, infections and neurotoxicity leading to increase risk of seizures in patients with low cholesterol. Depending on patient's nutritional status and duration of therapy, prophylaxis against *Pneumocystis carinii* and *Aspergillus* is required (28, 29).

1.2.2.6 Infliximab

Infliximab is an anti-TNF monoclonal antibody with potent anti-inflammatory effects. It is effective in both active and fistulating CD refractory to steroids and other first line immunosuppression. Associated side effects include joint pains and stiffness, fever and myalgia but infection is a risk, notably reactivation or development of TB. Indeed there is four to five fold increase risk of TB during this therapy. Infliximab can exacerbate existing cardiac failure and there is theoretical risk of inducing lymphoproliferative disorders or malignancies (30, 31) (Table 3).

Group	Mechanism of action	Minor side effects	Major side effects
Amino salicylates	Effects on epithelial cells	Headache, nausea, epigastric pain diarrhea	Idiosyncratic reactions (Steven Johnson syndrome, pancreatitis, agranulocytosis or alveolitis)
Corticosteroids	IL transcription, arachidonic acid metabolism	Cosmetic, sleep disturbance, mood changes, dyspepsia, glucose intolerance	Osteoporosis, myopathy, infection
Thiopurines	Pro –apoptotic and anti metabolite	Hepatotoxicity, pancreatitis	Myelotoxicity Malignancy/Lymphomas
Methotrexate	Anti metabolite and anti folate	Nausea, vomiting, diarrhea, stomatitis	Hepatotoxicity Pneumonitis
Cyclosporine	Prevent clonal expansion of T cells	Headache, dizziness, Acne, increase hair growth	Renal impairment, neurotoxicity, infection, seizures
Infliximab	Anti TNF monoclonal antibody	Fever, myalgia, joint pains, stiffness	Cardiac failure, TB, lymphoproliferative disorders

Table 3: Medical therapy used in IBD and common side effects.

1.2.2.7 Surgery

Surgery is usually advised for symptomatic disease not responding to intensive medical therapy. The decision to undertake surgery in CD is usually not may be protracted: these are usually symptomatic patients who have developed resistance to medical therapy or patients with complications. It should be remembered that surgery is not curative in CD-there is a high risk of disease recurrence. The commonly performed surgical procedures differ between UC and CD. In CD where it is important to preserve gut length, resection of bowel is usually limited to macroscopic abnormal segments, while in acute fulminant UC subtotal colectomy with or without primary anastomosis or total proctocolectomy with ileal pouch formation is performed. Many surgical operations in IBD are staged procedures involving formation of defunctioning stoma. Unlike in CD, surgery for UC is curative but clearly is a major life changing undertaking (3, 32).

To achieve optimal results, the timing of surgery is crucial. Early surgery may be unnecessary and premature while delayed decisions can increase morbidity and mortality and poor outcome (33). The effects on long term quality of life cannot be underestimated, for example the, change in body image following a permanent stoma. Restorative panproctocolectomy with ileal pouch formation however can improve the quality of life with significant high degree of satisfaction (34) although bowel emptying is usually altered for life (35). Complete assessment of extent and severity of disease is fundamental prior to any decision to undertake surgery.

1.2.3 ASSESSMENT OF IBD

The impact of IBD is disproportionately high on society for its prevalence due to chronic ill health of the young population affected. It remains a diagnostic and therapeutic challenge given is often uncertain and unpredictable course, and variable responses to medical and surgical management. IBD is a lifelong condition and patients must undergo repeated examinations to assess current disease extent and activity. It is therefore important that such examinations cause as little disruption, risk and discomfort to patients as possible. Even now, there is not one simple test that fulfills all the needs of the clinician in assessing patients with IBD and gastroenterologists in routine practice use combination of clinical assessment, numeric clinical indices, endoscopic findings and imaging modalities for this purpose.

1.2.3.1 Clinical activity scores

1.2.3.1.1 The Crohn's disease activity index (CDAI)

The CDAI was developed and validated in 1976 and consists of eight variables (36). The index ranges from 0-600 and the cut off between remission and active disease originally taken to be 150 while values above 450 indicating active and very severe disease. In later work 150 -219 was defined as mildly active and 220-450 as moderately active disease (Table 4).

Variable	Description		Multiplier
No of liquid stools	Sum of 7 days		X2
Abdominal pain	Sum of 7 days ratings	0- None 1- Mild 2- Moderate 3- Severe	X5
General well being	Sum of 7 days ratings	0- Generally well 1- Slightly under par 2- Poor 3- Very poor 4- Terrible	X7
Extra intestinal complications	No of listed complications	Arthritis/arthritis, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/ abscess, fever > 37.8 °C	X20
Antidiarrheal drugs	Use in the previous 7 days	0-no 1-yes	X30
Abdominal mass		0-no 1-questionable 5- definite	X10
Hematocrit	Expected-observed Hct	Males- 47 observed Females- 42 observed	X6
Body weight	Ideal/observed ratio	[1-(ideal/observed)] x100	X1 (NOT < -10)

Table 4: The Crohn's Disease Activity Index CDAI

Although the CDAI is one of the mostly used clinical indices particularly in the context of clinical trials it has undoubted limitations including

- Interobserver variability of symptom reporting between patients
- High weighting of scores of “general well being” and intensity of ‘abdominal pain’ - which are subjective.
- The calculation requires diary keeping by patients for 7 days, compliance is an issue in every day practice.
- Misleading results in n fistulating and stenosing disease.
- Limited utility in patients with n previous ileo- colic resection and stoma.

1.2.3.1.2 Simple Clinical Colitis Activity Index

This score consists of five clinical criteria and has shown positive correlation with laboratory markers (albumin, Hemoglobin, platelet count, hematocrit and ESR) and more complex scoring system such as Powel – Tuck Index (37) (Table 5).

Symptoms	Score
Bowel frequency (day)	
1-3	0
4-6	1
7-9	2
>9	3
Bowel frequency (night)	
1-3	1
4-6	2
Urgency of defecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extra colonic features	1 per manifestation

Table 5: Simple Clinical Colitis Activity Index

1.2.3.1.3 Other clinical activity indices

The Simple Index (Harvey Bradshaw index), the Organization Mondiale de Gastroenterologie (OMGE) index and the Cape Town Index have all been shown to correlate with each other and also with CDAI (38-40).

All the clinical indices can at best only give indirect assessment of disease activity. Furthermore they are rather complex and time consuming to collate. Use is therefore mainly limited to clinical trials.

1.2.3.2 **Biochemical Markers of activity**

The ideal biochemical marker in IBD should:

- Be helpful in identifying patients at risk
- Be disease – specific
- Be able to monitor disease activity
- Be simple
- Minimally invasive.

1.2.3.2.1 ESR- Erythrocyte sedimentation rate

The ESR is a widely used marker of acute phase response, as it provides crude and rapid although indirect assessment of plasma protein alterations during the acute phase response. The correlation between disease activity and ESR is good in UC and colonic CD but relatively poor in small bowel CD.

ESR levels are not only influenced by size, shape and number of erythrocytes but also by immunoglobulin level so its assessment is not disease specific. Changes in ESR in response to therapy often lags behind clinical response, which limits utility for patient follow up in routine practice (41, 42).

1.2.3.2.2 Acute phase proteins

Classical acute phase proteins are CRP, fibrinogen, serum amyloid A and orosomucoid (α_1 – acid glycoprotein).

CRP - is one of the most important acute phase proteins, produced exclusively in hepatocytes in response to stimuli including infections, inflammation, stress, tissue necrosis, trauma and childbirth. Its production is influenced by IL-6 and TNF and it has half life of 19 hours with baseline concentration of 0.8mg/L.

CRP and orosomucoid correlate with the disease activity in IBD but the 5-day half life of orosomucoid limits its use. Conversely CRP, has shorter half life, and often increases in the presence of active disease before rapidly decreasing after improvement in inflammation. Its levels are not directly affected by administration of anti inflammatory or immunosuppressive drugs (43).

CRP correlates reasonably well with CDAI in CD (44, 45). Supporting its use as a prognostic marker to assess treatment response. A rise in CRP is commonly seen with moderate to severe clinical activity in CD and there is reasonable correlation with other biomarkers (ESR, thrombocytosis, anemia and hypoalbuminemia) and endoscopic findings. However the correlation between CRP and radiological and histologic markers of disease activity is less robust (44, 46).

1.2.3.2.3 Leucocytes and platelets

Due to increase in polymorphonuclear leukocytes there is commonly a rise in white cell count in IBD but this remains a non specific marker of inflammation.

Platelet count correlates with disease activity both in UC and CD and also with CDAI in CD (47). As platelets have wide normal range and can be affected by other factors such as hemorrhage use is not widespread in clinical practice for monitoring disease activity in IBD.

1.2.3.2.4 Faecal Calprotectin

Calprotectin is calcium binding neutrophil protein, which stays stable during intestinal transit. It is stable in stool sample for up to 7 days at room temperature. It can be easily assessed in stools by ELISA test and has reported sensitivity of 95%, specificity of 93%, positive predictive value 95% and negative predictive value 93% to detect colorectal inflammation (48). It can reduce the number of endoscopies required to make diagnosis for IBD as normalized concentration indicates mucosal healing (49), but false negative results can lead to delayed diagnosis and treatment.

1.2.3.2.5 Albumin

Serum albumin levels reduce in active disease due to protein loss in gut and malnutrition (50) and extremely low levels has prognostic value in predicting medical treatment failure in UC.

1.2.3.2.6 Neopterin

Neopterin is marker of T cell, monocytes and macrophage stimulation in disorders like infections, inflammatory, autoimmune and malignant diseases. Its level in urine and serum is elevated in CD and UC but these high levels are not IBD specific so can only be used as an additional tool(51, 52).

1.2.3.2.7 B₂– Microglobulin

B2-microglobulin is a low molecular weight protein and higher serum levels reflect increased release from activated T cells and neutrophils (53). It is a sensitive indicator of renal function but serum level also rises in conditions like malignancies, liver diseases, sarcoidosis, cardiomyopathy and coeliac disease (54, 55).

Limited work has been done to assess its use as disease activity marker in IBD and to date no correlation has been found in its serum levels and clinical disease activity in UC (55) but results are a little more promising in CD (56, 57).

1.2.3.2.8 ANCA/ASCA

Antineutrophil cytoplasmic IgG antibodies (ANCA) are found in chronic inflammatory conditions like rheumatoid arthritis and UC, particularly the perinuclear type (pANCA). However, no apparent correlation between the presence and titer of pANCA and IBD duration, activity, localization, patient, age, sex or treatment response. A positive pANCA is found more commonly in UC compared to CD (58).

Another group ASCA (anti-Saccharomyces cerevisiae antibodies) are emerging as serological markers of CD and in contrast to pANCA it can reflect disease activity as reduction in serum levels is seen after resection of diseased bowel. It may have a role in identifying individuals at risk of developing IBD (58, 59).

1.2.3.2.9 Cytokines

Proinflammatory cytokines such as TNF- α , interleukin-1, interleukin-1ra, interleukin – 2R and interleukin 6, are produced by activate phagocytes and play an important role in the chronic inflammatory process. Increased numbers of TNF- α secreting cells are found in inflamed mucosa and treatment with anti-TNF antibodies in both CD and UC is now standard therapy in IBD patients refractory to conventional medical therapy has shown promising results (60-62). The use of the cytokines as markers of disease activity is not yet promising; there are large inter individual variations in the serum levels.

IL- 1 is a pro inflammatory cytokine and IL- 1ra is IL-1 receptor antagonists. Several studies have shown a decrease in the IL-1ra/IL-1 ratio with increase in active IBD, perhaps implicating a deficiency in endogenous IL-1ra in pathogenesis of IBD (63).

1.2.3.2.10 Cell adhesion molecules

Cell adhesion molecules (CAMs), are expressed by immune cells, endothelial cells and epithelial cells and some soluble forms are found in blood. Significantly higher levels have been reported in active CD and UC compared to inactive disease and these higher levels have shown correlation with CRP as well (64-67).

Significant overlap is seen between UC and CD, and indeed between IBD and controls and between active and inactive disease, making them poor markers of IBD activity. In addition, their measurement is difficult and overall they do not easy and convenient and do not appear to add any significant information regarding disease management.

1.2.3.3 Colonoscopy

Since 1970's colonoscopy has become the gold standard for the diagnosis of IBD (68-70). Examination of whole colon and multiple random biopsies during colonoscopy in clinically suspected cases able to make diagnosis of IBD in 80-90% of affected patients (71, 72) and in around 90% it is able to help differentiate between CD and UC (73).

Colonoscopy requires full bowel preparation, usually with oral laxatives and during procedure the majority of patients receive sedation. The endoscopist maneuvers the colonoscope within the bowel, using air or carbon dioxide for distension while monitoring progress on a video screen. Endoscopy requires considerable operator skill and extensive training is mandatory.

The endoscopic features of IBD include friable mucosa, spontaneous bleeding, aphthoid ulcerations, cobblestone appearance and stenosis (74). Endoscopy is regarded as the most accurate modality for the assessment of the extent and the severity of disease, although clearly it is unable to visualize the small bowel beyond the terminal ileum. Luminal stenosis may also limit endoscopic examinations. Endoscopy provides exquisite images of the enteric mucosa but in the presence of systemic manifestations and transmural inflammation, endoscopic features do not always correlate with clinical and biochemical markers (8).

Further limitations include technically difficult examinations for example in patients with, long mobile or tortuous colon leading to, patient discomfort. Poor bowel preparation can lead to difficult or incomplete colonoscopy in 17-23% of cases (75, 76).

There is a small but well recognized risk of bowel perforation during colonoscopy of 0.03-0.19% (77-79), with some data that it may be higher in IBD patients (80, 81).

Surgery following endoscopic perforation has an associated mortality (82, 83).

Patient experience of colonoscopy may be somewhat negative with the rigors of bowel preparation, procedural discomfort, and embarrassment. There is however evidence that familiarity with colonoscopy does reduce patient concerns during subsequent repeat procedures (84). Gas insufflation and colonic manipulation are the main reasons for discomfort, although sedation undoubtedly lessens procedure related pain. The use of sedation does risk hypoxia and cardiac arrhythmias, particularly in vulnerable patients and necessitates patient monitoring during the procedure by trained staff together with provision of post procedure recovery facilities

Various scoring endoscopic scoring systems for assessing disease severity and activity have been developed over time, notably the Crohn's disease endoscopic index of severity (CDEIS), Endoscopic Crohn's disease index (SES-CD) and Rutgeert's score.

1.2.3.3.1 Crohn's Disease Endoscopic Index of Severity (CDEIS)

This scoring system was developed in 1989 by French group of GETID (Groupe d'Etude Therapeutique des Affections Inflammatoires Digestive) (85). It is based upon the presence or absence of four types of lesion (superficial ulcers, deep ulcers, ulcerated stenosis and non ulcerated stenosis) and the score can range from 0 to 30. Over time it has become established as the gold standard for endoscopic evaluation of activity. It is

a reliable and reproducible scoring system, although has shown poor correlation with clinical disease activity in some therapeutic trials (85, 86).

Given the time consuming and relatively complex nature of the scoring system, use in every day clinical practice is limited (Table 6).

Rectum Sigmoid & left C Transverse C Right C Ileum	Total
Deep ulcerations (12 if present)	Total 1
Superficial ulcerations (12 if present)	Total 2
Surface involved by disease (cm)	Total 3
Surface involved by ulcerations (cm)	Total 4
Total 1 + Total 2 + Total 3 + Total 4=	Total A
Number of segments totally or partially explored	n
Total A/n=	Total B
If an ulcerated stenosis is present anywhere add 3=	C
If a non ulcerated stenosis is present anywhere add 3=	D
Total B + C + D=	CDEIS

Table 6: Crohn's Disease Endoscopic Index of Severity

1.2.3.3.2 Endoscopic Crohn's disease index (SES-CD)

SES-CD is based of four endoscopic variables (ulcer size, ulcerated and affected surface, stenosis) scoring 0-3 in five ileocolonic segments (Table 7& 8).

SES-CD: sum of all variable – 1.4 x (number of affected segments)

Data has shown the score is reproducible but shows weak correlation to clinical indices (SES-CD to CDAI $r = 0.371$ and SES –CD to CRP $r = 0.453$), likely due to its inability

to account for systemic or fistulating disease and involvement of proximal segments not visualized at CC.

It is simple and faster to calculate as compare to CDEIS but again use is limited in every day endoscopic assessment (8).

Variables	0	1	2	3
Presence of ulcers	None	Aphthous ulcers (0.1-0.5 cm)	Large ulcers (0.5-2 cm)	Very larger ulcers (>2cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed
Number of affected segments	All variables =0	At least one variable ≥ 1		

Table 7: SES- CD variables

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Sum
Presence of ulcers						+
Ulcerated surface						+
Affected surface						+
Presence of narrowing						=
					Sum of variables	TOT
Affected segment					TOT- 1.4 x (number of affected segments)=	E-CDI

Table 8: SES-CD scoring

1.2.3.3.3 Rutgeert's Score (Table 9)

The Rutgeert's score is generally accepted as the gold standard endoscopic score for assessment and prediction of post surgical disease recurrence. It has five grades of endoscopic severity. Studies have found it useful in revealing signs of recurrence in 60-70% patients within 6-12 months of surgery and also in predicting the course of disease. For example mild endoscopic recurrence (<5 aphthous ulcers) within 1 year of resection shows a clinical relapse rate of 9 % at 7 years, whereas, severe endoscopic recurrence commonly have clinical relapse at 4 years (87, 88). It is useful in providing guidelines in further management of such patients or can be used in therapeutic trails to assess mucosal healing as a trial end point (89). It does not take into consideration involvement of deeper layers, perimesenteric inflammation and the extra mural complications.

Grade	Endoscopic findings
I ₀	No lesion in distal ileum
I ₁	≤ 5 aphthous lesions
I ₂	> 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions confined to ileocolonic anastomosis
I ₃	Diffuse aphthous ileitis with diffusely inflamed mucosa
I ₄	Diffuse inflammation with already larger ulcers, nodule, and / or narrowing.

Table 9: Rutgeert's score

There is no single scoring system used widely in every day endoscopic disease assessment. In addition, the use of CC in acute exacerbation of disease or to assess effectiveness of medical therapy is still not fully defined.

1.2.3.3.4 Mucosal Healing (MH)

In 2007, the International Organization of IBD proposed a definition of Mucosal healing in UC “the absence of friability, blood, erosions and ulcers in all visualized segments of gut mucosa”. It signifies complete healing of all inflammatory and ulcerative lesions seen on endoscopy and not just a change in CDEIS or SES-CD after treatment (90).

In UC, where disease is largely limited to the mucosa, mucosal healing is in theory the ultimate therapeutic goal, whereas in CD, a transmural process, it arguably is a minimal therapeutic aim. Mucosal healing can be used an objective end point in therapeutic trials and in clinical practice is a strong predictor for improve outcome of treatment. Long

term maintenance of mucosal healing may decrease structural damage to the bowel, thereby resulting in fewer complications and fewer surgical interventions.

The routine use of endoscopy in patients with complete clinical and biological response to treatment is not advocated. Total disappearance of all the mucosal ulceration is relevant end point for therapeutic trials but its use in day to day clinical practice remains uncertain. The macroscopic evaluation of colonic mucosa at endoscopy is insufficient to completely assess disease activity and histological inflammation can exist in the face of seemingly normal mucosa.

Furthermore it is not clear at present whether MH truly reflects resolution of transmural injury of the wall in CD (91, 92).

1.2.3.4 Barium Fluoroscopy

Radiological imaging plays a key role in the diagnosis and management of patients with suspected or proven IBD. Barium fluoroscopy has been used for many years to assess small bowel disease (either using barium enteroclysis or barium follow through techniques) as well as for colonic disease using as the barium enema.

Small bowel enteroclysis (SBE) and small bowel follow through (SBFT) are the traditional radiological techniques used for assessment of small bowel morphology.

Both enable direct visualization of bowel lining, width of lumen and stenosis, range of affected segments and presence of complications. In experienced hands, they have similar sensitivity of 85-95% and specificity of 89-94% in detecting radiological signs of CD (93). Patients usually prefer SBFT as no nasal or oral intubation is involved. It is associated with less radiation exposure, is less time consuming and less expensive (94).

The barium enema was first described by Fishcer in 1923 and was refined in 1960's and 1970's. It has been the radiological investigation of choice for the colon (8, 75). It can be performed in two main ways, as a single contrast study using barium alone, or as a double contrast (DCBE) in which gas is insufflated into the colon so that lesions are outlined by a gas-barium interface. The vast majority of studies performed in the United Kingdom utilize the double contrast technique.

Barium enema requires full bowel preparation, usually with oral laxatives. Sedation is not generally needed although antispasmodic medication is usually administered (95). Colonic distension is achieved using air or carbon dioxide, and there is good evidence that the latter results in less patient discomfort (96). The passage of barium and gas into the colon is monitored fluoroscopically and an adequate examination necessitates significant movement of the patient during the procedure, which may be difficult in the elderly or infirm.

The barium enema has played a key role in diagnosis and management of IBD patients (97) and is still used as additional tool in cases of incomplete or difficult CC (98, 99). A well performed barium enema can detect very early mucosal changes such as aphthous ulceration and when it comes to differential diagnosis of CD and UC, it has a sensitivity of sensitivity of 95-98% (100).

Akin to CC, barium enema is an operator dependent invasive modality although the reported incidence of bowel perforation is only 0.02 -0.04 % (101). Only assessment of the lumen is generally achieved and transmural extension of CD and extra luminal complications are usually missed. The technique also uses ionizing radiation with total effective dose up to 10.7 mSv from a single examination (102, 103).

1.2.3.5 Ultrasonography in IBD

Ultrasonography is easily accessible, inexpensive, non-invasive, painless diagnostic tool with the potential widespread clinical use due to ubiquity of ultrasound equipment throughout the NSH. It provides information about the bowel wall and extra – intestinal manifestations of disease.

The typical feature for diagnosis of IBD include

- Bowel wall thickening (> 3 mm)
- Presence of a “stiff” bowel wall (reduced peristalsis)
- Modification or disappearance of bowel wall stratifications in CD and preservation of stratification in UC
- Presence of deep ulcers – interruption of the submucosal hyperechoic rim by a hyperechoic tract
- Loss of haustrations and tubular appearance of colon in long standing disease
- Extra mural features – fibrofatty proliferation, enlarged lymph nodes, abscess or fistulae (104-106).

Reported sensitivity of US for diagnosis in suspected cases of IBD is 76- 92% while in patients with known disease, it is higher (107-109) and correlates well with endoscopic features of active disease (110) . It can also accurately detect extra mural complications, fistulae, and abscesses. Doppler US has also been used to distinguish between active and inactive disease (111, 112).

Jejunal or duodenal disease is often missed using US, while the rectum and distal sigmoid are not visualized fully due to their pelvic location. US with enteral contrast have shown higher sensitivity for diagnosis of both small bowel and colonic disease,

and even detection of jejunal lesions (113-115) but the spatial resolution of US is not high enough to detect the early and superficial mural disease.

US is extremely operator –dependent and requires skilled staff with expert knowledge of IBD. It is difficult to perform on overweight patients as adipose tissue attenuates the ultrasound beam.

1.2.3.6 CT Enterography (CTE) and CT Colonography (CTC)

Computer tomography imaging offers many advantages in assessment of CD-wide spread availability, high sensitivity and specificity for detection of luminal and extra luminal disease, rapid acquisition of images with high spatial and temporal resolution and short overall acquisition time.

CT Enterography and CT Enteroclysis are modification of conventional CT technique optimized for the evaluation of small bowel by administration of large volume of enteric contrast agent either orally (CT Enterography) or through a nasojejunal catheter (CT enteroclysis).

In suspected cases of IBD CTE has sensitivity of 83% in comparison to SBE and 80-88% compared to endoscopy (116-119). For detection of disease and in cases of known IBD it has a sensitivity of 80-90% and specificity of 90-98% in comparison to endoscopy, SBE and surgery. In general CT is not accurate in detection of early superficial lesions (97).

CT Colonography was described in 1994 by Vining et al, as a relatively non invasive and rapid whole colon examination (69). It has advantage of visualizing both luminal and extraluminal disease.

Typical IBD findings on CT include

- Segmental wall thickening (“target” or “double halo” appearance)
- Hyperenhancement after IV contrast- a direct expression of transmural inflammation
- Small bowel wall stratification (visualization of two or three layers of bowel wall)
- Sub mucosal fibro fatty infiltration
- Stenosis and pre stenotic dilatation
- Mesenteric fat edema
- Pericolic mesenteric inflammation
- Engorged ileal vasa recta (comb sign)
- Lymphadenopathy
- Inflammatory phlegmons and abscesses

Studies have reported 80-90 % sensitivity for detection of extraluminal complication such as fistulae, sinuses and abscesses (11). CTC is well tolerated by patients as compared to barium enema or colonoscopy (72, 120) and there is no need to use sedation.

The use of both CT Colonography and CT Enterography is limited given the exposure of the generally young IBD patient cohort to ionizing radiation. There is a theoretical risk of cancer induction even at the relatively low doses of diagnostic imaging (10). Indeed some suggest 0.7-2% of all cancers and 1% of all cancer related mortality due to radiation exposure from CT abdomen and pelvis (121, 122). The effective radiation dose to colon from a CTC and CTE is similar to standard CT abdomen and pelvis,

(around 13. 2 mSv per study). In theory the risk of inducing cancer is even higher in patients with IBD given their need for repeat imaging over the course of their disease and thus the cumulative radiation exposure during their life time (10). Attempts have been made to reduce radiation dose at CT by reducing the tube current but reducing the tube current to 30 mAs although image quality is reduced (123) (Table 10).

	Colonoscopy	DCBE	CTC
Sensitivity for IBD diagnosis	80-90%	90-94%	80-90%
CD/UC	89%	95-98%	Na
Perforation risk	0.03-0.19%	0.02-0.04%	0.04-0.05%
Extraluminal disease evaluation	No	No	Yes
Radiation exposure	No	Yes	Yes

Table 10: Comparison of CC, DCBE and CTC

CTC is not recommended as first line examination when superficial mucosal disease is suspected and is clearly contra indicated in acute colitis/toxic megacolon due to the risk of perforation.

1.2.3.7 MREnterography (MRE) and MRColonography (MRC)

The use of MRI in IBD has dramatically risen in recent years due to the lack of ionizing radiation exposure and superior tissue contrast in comparison to conventional fluoroscopy and CT. Advances in MRI hardware and sequences mean high quality images of the bowel can be acquired with the time of a single breath hold. MRI was initially used for evaluation of perianal disease where it has now become the gold standard in the evaluation of IBD related perianal sepsis, surpassing examination under anesthetic and improving surgical outcomes.

Its use in evaluating small bowel and colonic disease is now rapidly evolving. An exciting facet of enteric MRI is the potential to not only diagnose and stage IBD, but also to accurately assess disease activity. Various parameters including bowel wall thickening, bowel wall hyper intensity and hyperenhancement, lymphadenopathy and mesenteric inflammation have all been linked to active disease. In terms of technique, MRI Enterography/ Enteroclysis involves distension of the small bowel with fluid either ingested or infused via nasojejunal tube. MR Colonography requires distension of the colon with fluid or gas, usually after some form of bowel preparation

In common with all cross sectional imaging techniques, MRI facilitates examination of the bowel wall and the extra enteric tissues-mesenteric fat stranding, mesenteric hypervascularity abscess and fistula formation, and fibro-fatty proliferation are all well seen (124, 125).

Section 1.3 further explores the role of enteric MRI in IBD

1.3 MAGNETIC RESONANCE IMAGING IN IBD

1.3.1 BACKGROUND

Magnetic resonance imaging has arguably become the most important development in medical diagnosis since the discovery of roentgen ray more than 100 years ago. With the development of fast imaging sequences and specialized surface coils indications now extend to every part of body.

Up until the relatively recent past, the use of MRI for the assessment of enteric disease was limited because of artifacts secondary to respiration and bowel peristalsis, prolong imaging time and poor contrast resolution. However over time, technical advances have overcome these limitations and high resolution breath hold imaging is now routine. A significant advantage of MRI over CT is its lack of ionizing radiation use. This is particularly pertinent in the younger population affected by IBD who may need repeated imaging during the course of disease. Over and above this advantage, MRI affords superior contrast resolution to CT allowing additional diagnostic information not possible with X-Ray based technologies

A more thorough review of the literature pertaining to MRI is given below, but it is interesting to briefly describe some of the early data, which paved the way for the development of enteric MRI. As far back as 1993 Shoenut et al (126) compared MRI findings with endoscopy and surgical findings in 28 patients with known IBD. MRI findings were used to categorize bowel inflammation into mild, moderate and severe. Using a system based on the length of disease, wall thickness and contrast enhancement, Shoenut reported a significant correlation between endoscopic/ surgical findings and all these MRI parameters. Just one year later the same authors (127) studied patients with clinical suspicion of IBD who underwent had MRI and colonoscopy. They found no

significant difference between modalities for the assessment of disease severity ($p > 0.05$) and for differentiating between CD and UC ($p > 0.05$). In this exploratory work, MRI was considered comparable to endoscopy for determination of disease severity and to distinguish between UC and CD. This work undoubtedly stimulated the wealth of research, which has now taken place in this field and raised the profile of enteric MRI, which was hitherto relatively ignored.

MRI evaluation of bowel can be undertaken using standard 1.5T or 3T MRI with and usually uses multichannel phase array coils. Three imaging sequences form the backbone of MRI protocols. A single shot fast spin echo T2 sequence with half-Fourier reconstruction (HASTE) allows detailed evaluation of the bowel wall and adjacent mesentery. The sequence can be disrupted by peristaltic flow artifacts and is best employed after spasmolytic administration. A balanced steady state free precession (True FISP) is less sensitive to motion artifact and allows evaluation of the bowel wall, although its particular strength lies in assessment of the adjacent mesentery; hypervascularity, fibrofatty proliferation and fistulae all are well seen. The third sequence is a dynamic fast 3D spoiled gradient echo T1 fat-suppressed post intravenous gadolinium sequence (VIBE) to evaluate the extent and pattern of bowel enhancement (12, 128). As detailed later in this thesis, additional sequences, notably diffusion weighted imaging are showing considerable promise over and above this basic sequence complex.

1.3.2 MRI IN SMALL BOWEL

MRI evaluation of the small bowel typically combines large volume enteric contrast distention of bowel with rapid breath hold T2 and post contrast T1 weighted images in the axial and coronal plane (129). Bowel distension is in general a pre-requisite to enteric MRI. By distending the bowel, it is possible to evaluate the inner and outer

borders of the bowel wall and much better appreciate wall thickening, abnormal enhancement and mural signal changes. Such changes are much more difficult to appreciate if the bowel is collapsed. Indeed inadequate distension is one of the most common causes for failed MRI Enterography. As discussed below, some workers advocate the use of MR Enteroclysis-small bowel distension being facilitated by infusion of contrast through a nasojejunal tube. Although quality of distension is superior to MRI Enterography particularly in the proximal bowel, patient compliance is less and in general, MR Enterography is the workhorse of small bowel MRI imaging. With its ability to assess disease activity and distribution, and diagnose complications as obstruction, perforation, strictures and abscesses, MRI of the small bowel is increasingly indicated for first diagnosis of IBD, suspected disease relapse, assessment of treatment failure and before planned surgical resection (130).

Enteric contrast agents used are divided into three groups (131).

- Positive agents:

These demonstrate high signal intensity on T1 and T2 images and are helpful delineating the bowel wall. Examples are blue berry and pineapple juice, diluted gadolinium and milk with high fat content. In general, positive agents are rarely used in clinical practice.

- Negative agents:

Negative agents have low signal intensity on both T1 and T2 weighted images, and include oral superparamagnetic iron oxide particles. They provide better visualization of bowel wall edema and mucosal enhancement and help to discriminate between intraluminal and extraluminal fluid (abscess). Advocated

by several European groups, negative contrast agents tend to have a less pleasant taste compared to other agents and are more expensive (132).

- Biphasic agents:

Biphasic agents have low signal intensity on T1 weighted images and high intensity on T2 weighted sequences. Examples include water, polyethylene glycol, diluted barium with sorbitol (2%) and mannitol (2.5%), mannitol (2.5%.) with locust bean gum (0.2%). The high signal on T2 weighted images facilitate delineation of the bowel wall, whilst the low signal on T1 weighted images allows better appreciation of contrast enhancement. Although water has biphasic properties, in reality it is a very poor oral contrast agent prior to enteric MRI as it is quickly absorbed and bowel distension is poor. Biphasic agents used in clinical practice therefore all have hyperosmolar properties such they resist absorption by the bowel and remain in the lumen, maximizing distension. Hyperosmolar agents, such as polyethylene glycol, mannitol (with or without locust bean gum) and the most widely used agents in clinical practice are among this group (133). There is some evidence that a combination of mannitol (2.5%) and locust bean gum (0.2%) provides the best bowel distention (134, 135) but all such agents can cause hyperosmolar diarrhea.

	Positive agents	Negative agents	Biphasic agents
Single characteristics	High signal intensity on T1 & T2 weighted images	Low signal intensity on T1 & T2 weighted images	Low signal intensity on T1 High signal intensity on T2 weighted images
Typical examples	Diluted Gadolinium Blue berry juice Pineapple juice Milk with high fat	Superparamagnetic iron oxide particles Ferumoxsil	Water Polyethylene Glycol Barium with sorbitol Mannitol Mannitol with locust bean gum VoLumen
Other features	Pleasant taste	Unpleasant taste	Hyperosmolar diarrhea

Table 11: Comparative qualities of enteric contrast agents

As noted above, enteric contrast agent is administered either orally (MR Enterography) or through nasojunal tube (MR Enteroclysis).

1.3.2.1 MR enteroclysis

This method involves transnasal or oral placement of a balloon tipped catheter into proximal jejunum under fluoroscopic guidance or MRI real time guidance.

1.5-2L of enteric contrast is then infused in a controlled fashion to distend the bowel. The tube balloon can be inflated to prevent the reflux of fluid into stomach. The high

filling volume leads to secondary paralysis of the small bowel and helps avoid motion artifacts although additional antiperistaltic agents are usually used.

1.3.2.2 MREnterography (MRE)

MREnterography is the more commonly performed alternative to enteroclysis and has better patient compliance. The patient drinks up to 1.5 l of the oral contrast agent over the 40-45 minutes before procedure. Although good quality images can be acquired with ingested volumes below 1l, active encouragement of the patient is important to ensure compliance with the drink regimen.

MRI imaging can be performed either in the prone or supine position, although the prone position has some advantages; abdominal compression reduces the length of breath hold required for image acquisition. Supine position is adequate for patients with stomas, enterocutaneous fistulae and for those who cannot lie prone.

1.3.2.3 Imaging protocol

Although there are variations in a clinical practice, a typical MREnterography protocol is given below

Protocol for MREnterography (135)

Metoclopramide 20 mg orally

Mannitol (2.5%) and locust bean gum (0.2%) 150mL orally every 4 mins, total 1.5L

Image at 40-60 min

Thick – slab T2 weighted MR (optional)

Coronal and axial gradient – echo T2- weighted FISP sequence

Hyoscine butylbromide 10 mg or glucagon 0.2 mg IV

Axial and coronal single shot fast spin echo T2 sequences with half-Fourier reconstruction with and without fat suppression

Coronal 3D unenhanced T1- weighted FLASH (VIBE) sequences

Hyoscine butylbromide 10 mg or glucagon 0.2 mg IV

Coronal 3D gadolinium – enhanced T1-weighted FLASH (VIBE) sequences with 30-70 sec delays

Axial 3D T1- weighted FLASH sequence at 90 sec.

MR Enteroclysis	MR Enterography
Invasive procedure	Non invasive
Poor patient compliance	Better patient compliance
Logistically challenging due to time required for placement of nasojejunal catheter and bowel distension	More time efficient.
Better for diagnosis of suspected jejunal disease. Depict early disease and number of disease segments.	Suboptimal distension of jejunum and false negative or false positive findings due to incomplete bowel loop distention
Less intraluminal artifacts	Intraluminal flow artifacts mimic cobblestoning

Table 12: Comparison of MR enteroclysis and enterography (136, 137)

1.3.2.4 Enteric findings

Typical features of IBD include (12, 135, 138, 139)

1.3.2.4.1 Thickening of wall of diseased segment

Wall thickness more than 3 mm in distended small bowel loop is abnormal, it usually ranges between 5-10mm and is accurately assessed with HASTE sequences. Wall thickness is usually greater in CD as compare to UC due to transmural inflammatory process.

1.3.2.4.2 Abnormality in mucosal folds

- Picket fence pattern of diffusely thickened folds
- Reduction or distortion of folds due to ulceration
- Cobblestoning- a patchy areas of both high and moderate signal intensity caused by longitudinal and transverse ulceration seen on true FISP images

1.3.2.4.3 Ulcerations

Moderate to deep ulceration can be seen as thin lines of high signal intensity within thickened bowel wall on HASTE images.

1.3.2.4.4 Strictures – with segment of thick wall

- Functional - stricture with upstream bowel dilatation greater than 3 cm
- Non functional - more than 10% narrowing in the lumen without dilatation

1.3.2.4.5 Wall edema

High T2 signal intensity particularly well seen on fat saturated HASTE images bowel

1.3.2.4.6 Mural enhancement

- Stratified or layered pattern- bright mucosa due to inflammation and hypoenhancing submucosa due to edema.
- Diffuse pattern- homogeneous enhancement of entire wall thickness due to transmural inflammation
- Low –level inhomogeneous enhancement- likely represent fibrosis

1.3.2.4.7 Pseudosacculation or Pseudodiverticulum

Fibrosis and shortening of diseased mesenteric wall cause dilatation of anti mesenteric border.

1.3.2.5 **Extraenteric findings**

1.3.2.5.1 Comb sign

Short low- signal intensity parallel lines on true FISP images and as high signal intensity lines on VIBE images due increased mesenteric vascularity during active disease.

1.3.2.5.2 Mesenteric edema

It is seen in advanced active disease. Increased mesenteric signal best seen on fat saturated T2 weighted images

1.3.2.5.3 Fat wrapping/ hypertrophy

Increased mesenteric fat causes displacement of mesenteric vessels or other viscera. It is a specific sign of CD, representing long standing transmural inflammation.

1.3.2.5.4 Lymph nodes

Hyper enhancement, enlargement and edema of lymph nodes adjacent to bowel seen on fat-saturated HASTE and TrueFISP images

1.3.2.5.5 Fistulas and sinuses

Seen as high signal intensity tracts on T2- weighted images or as enhancing tracts on post contrast enhanced T1 weighted sequences e.g. enterocolic, enteroenteric or enterocutaneous.

1.3.2.5.6 Abscess

As well defined, encapsulated collection of pus with high signal intensity on T2 – weighted and low signal intensity on T1 – weighted images typically with an enhancing rim. (131, 139).

1.3.2.6 Review of literature pertaining to MRI in Small bowel IBD

Over the time, significant amount of work has been undertaken regarding use of MRI (enterography & enteroclysis). Diagnostic accuracy of MRI has been compared to various reference standards and below is the summary of some of these.

1.3.2.6.1 Endoscopic Reference

Magnano and colleagues compared MRE, US and Doppler US using ileocolonoscopy as reference standard in children with known CD. MRE was performed after oral intake of polyethylene glycol solution. It depicted stenosis, thickening and hyperemia of bowel

wall. Concordance of MR and US for detection of wall thickening and increased vascularity was 95% and 80% respectively (140).

Florie et al (141) used water as intraluminal contrast medium and compared MRI with endoscopic grading of disease severity -CDEIS. Wall thickness correlated moderately to strongly with CDEIS ($r=0.57, p<0.001$ and $r=0.50, p<0.001$) while enhancement correlated weakly to moderately ($r=0.45, p<0.001$ and $r=0.42, p<0.001$). They also compared patient experience and overall preference. Patients found endoscopy more painful and hence, expressed preference for MRE as future investigation. In the same year, another study of MRE was performed at 3.0 T MRI and also used CDEIS as standard of reference (142). Only a weak to moderate correlation was found between bowel wall thickness and CDEIS and between wall enhancement and CDEIS. Again the majority patients preferred MRE to ileocolonoscopy.

Borthne and colleague (143) compared the sensitivity, specificity and diagnostic accuracy of MRE (300 mL mannitol in 15% water) and US to endoscopy in children with suspected IBD. They assessed wall thickness and contrast enhancement and found sensitivity of 81.8%, specificity 100% and diagnostic accuracy of 90% for MRE for CD. 50% of patients were willing to repeat the examination in future.

Diagnostic accuracy of MRE has also been compared to wireless capsule endoscopy (WCE). In one such study, Golder and colleagues detected the same number of inflammatory lesions in terminal ileum with both modalities but WCE detected additional lesions in proximal ileum and jejunum (12 vs. 1) whereas, MRE showed extra intestinal pathologies in 28% (144). Two years later, Tillack et al (145) also compared MRE with WCE but only in known patients with CD. Both modalities showed the same disease features in 56% segments but WCE detected more superficial

mucosal disease. However, MRE was better in diagnosing severe inflammatory mural changes.

Sailer et al proposed an MRE score for post surgical recurrence, based on image quality, contrast enhancement, mural and extra mural bowel wall changes to assess post resection recurrence in CD.

MR0	No abnormal features
MR1	Minimal mucosal changes
MR2	Diffuse aphthoid ileitis, moderate recurrence
MR3	Severe recurrence with trans and extramural changes

Table 13: MRE score by Sailer et al.

They used the previously validated Rutgreets score as a reference standard and high agreement was observed between MRE score and Rutgreets score (146).

The ability of MRE to precisely detect active small bowel disease has been compared with CTE by using endoscopy as reference standard. In one such study in 2009, (147) a similar sensitivity of 90.5% for MR enterography and 95.2% for CT enterography (p 0.32) was reported for detection of active disease and both modalities diagnosed additional disease in 24% of patients who had normal ileocolonoscopy. A few years later, Fiorino and colleagues (148) again used ileocolonoscopy as reference standard to compare both modalities and reported supremacy of MRE in the recognition of strictures (p=0.04).

1.3.2.6.2 Non endoscopic Reference

Several studies have used, non-endoscopic standards of reference, MRE being compared to various biomarkers and other imaging modalities in children as well as adults.

Schunk et al compared bowel wall enhancement on MRI after oral administration of 1L of 2.5% mannitol with CDAI and CRP and reported superiority of MRE in distinction of active and inactive stenosis (149) which is crucial in planning of treatment.

In the same year Miao et al (150) compared MRE with oral water with US against a combination of clinical assessment, endoscopy, barium study or surgery as reference standard and found equivalent sensitivity in detection of active disease (87%).

Laghi et al (151) derived an MRE score based on wall thickness and contrast enhancement in children with known CD use CDAI as a global reference standard together with ileocolonoscopy to evaluate disease activity in terminal ileum. They used polyethylene glycol as the oral agent. This score exhibited sensitivity of 84% and specificity of 100% for recognition of erosive ileitis seen on endoscopy.

Pilleul et al (152) in 2005 again verified positive correlation between bowel wall thickness and pediatric CDAI on MRE with 5% mannitol but no significant correlation was established with contrast enhancement. MRE also revealed fistulae (9), strictures (8) and intussusception (1) in these patients.

The role of dynamic contrast MRE to distinguish between active disease and remission was evaluated by Pupillo et al (153). They observed early and intense uptake of contrast which increased over time until a plateau was seen in diseased segments of bowel while in segments with remission uptake was less intense, although, still higher than normal

segments. A significant correlation was reported between the peak of contrast uptake and CDAI.

Taylor et al (154) also used dynamic contrast enhanced MRI to correlate with histopathological markers of inflammation and angiogenesis. Patients had pre operative MRI and slope of contrast enhancement, time to maximum enhancement, enhancement ratio, the volume transfer coefficient K (trans) and extracellular volume fraction v (e) for the diseased segment of bowel were measured and the resected specimen was re imaged. Acute and chronic inflammation scores and micro vascular density (MVD) were measured in resected specimen. They found a positive correlation between disease chronicity and enhancement ratio (correlation coefficient 0.82, $p=0.002$) but negative correlation between slope of enhancement and MVD (correlation coefficient -0.86, $p<0.001$), supporting the hypothesis of increased micro vessel permeability with disease chronicity and an inverse relation of tissue MVD to mural blood flow.

In 2009 Martinez and colleagues (155) compared MRE (sodium phosphate and water) and Doppler US with clinical scoring and biological tests. Contrary to the previously reported equivalent sensitivity of MRE and US for detection of active disease in 2002, they found US was more sensitive in localization of diseased segment (91%/83%) although grades of hyperemia and contrast enhancement on MRE were higher in patients with clinical-biological active disease, in comparison to patients without clinical –biological activity ($p=0.019, p=0.023$).

Zappa and colleagues in a retrospective study (156) compared the mural and extra mural findings of pre operative MRE with the pathological analysis in resected specimen in 53 known patients of CD. The MRE parameters significantly associated with inflammation were wall thickness, wall enhancement, pattern of enhancement, T2 relative hyper signal, blurred wall enhancement, comb sign, fistula and abscess.

1.3.2.6.3 Combined Endoscopic and non endoscopic reference

Low and colleagues used multiple reference standards including surgical, endoscopic and histological findings together with barium studies to compare MRI and CT. MRI was performed with 2% oral barium sulfate, rectal water and IV gadolinium while IV contrast enhanced CT was performed with positive and negative enteral contrast in equal number of patients. Based on wall thickness and contrast enhancement on MRE was found superior to CT in depicting disease (85% vs. 65% abnormal segments). It was not only better in depicting mild disease (79% vs. 49% segments) but also in delineating mural thickening (41% vs. 11% segments) and mural enhancement (89% vs. 11% segments) (157).

Koh et al (158) assessed bowel wall thickness, contrast enhancement and perienteric changes on MRE (with oral water) in comparison to CDAI, endoscopy and surgery. MRE had overall sensitivity of 91% and specificity of 71% on per patient basis while CDAI had sensitivity of 92% and specificity of 28% for active disease.

The ability of T2 weighted images to detect disease has been compared to contrast enhanced T1 weighted sequences. In such an attempt, Maccioni (139) compared the diagnostic accuracy of oral contrast enhanced T2 weighted imaging with T1 weighted gadolinium enhanced imaging using endoscopy, small bowel barium, CT, US and clinical biochemical scoring as references. The authors recommended combined use of T2 and T1 weighted imaging achieved better diagnostic accuracy.

After establishing diagnostic accuracy for IBD, further steps have been taken to gauge capacity of MRE to distinguish CD and UC. Horsthuis in 2010 reported superior

diagnostic accuracy of MRE in children for CD than UC (159) against the reference standard of (esophagogastroduodenoscopy & ileocolonoscopy) and barium enteroclysis.

1.3.2.6.4 Enterography vs. Enteroclysis

MR enteroclysis although more invasive than MRE has shown promising results.

Holzkecht et al (13) used oral magnetic particles in 18 patients with known CD before surgical intervention and showed a sensitivity of 95.8-100% for primary diagnosis of CD, 94.7% of stenosis and 100% for fistulae not to mention detection of complications such as abscesses and affection of ureter. Both MRI techniques have compared in suspected as well as known patients with CD. Negaard et al (160) compared MRE (6% mannitol) and MR Enteroclysis (polyethylene solution) in patients with suspected CD. They evaluated bowel distension, wall thickness, contrast enhancement, detection of ulcers, stenosis and edema. Bowel distension was better with MR enteroclysis although both had high diagnostic accuracy. MRE and MR enteroclysis both showed sensitivity of 88%, specificity of 89/84%, positive predictive value 89/82% and negative predictive value of 89%. The authors also compared patient experience of both modalities and found higher patient preference for MRE due to less abdominal pain and discomfort (137).

Masselli et al also reported better jejunal distention ($p < 0.01$) and detection of bowel wall abnormalities ($p < 0.01$) with MR Enteroclysis but MR enterography was more acceptable to patients (136).

1.3.2.6.5 MRI vs. Barium Studies

For years Barium studies have been the standard radiological investigation for assessment of the small bowel morphology. In 2000, Rieber et al (161) compared

conventional Barium enteroclysis and MR enteroclysis in 84 patients with histological and endoscopy correlation using wall thickness and detection of stenosis as diagnostic criteria. They reported a higher sensitivity and specificity with MR Enteroclysis 92.2% vs. 85.4% and 92.6% vs. 76.9% respectively. No abscesses were detected on SBE and only 17.7% fistulae were seen while 77.8% fistulae and 17.8% abscess were detected on MRE.

Bernstein et al (162) compared the findings of SBFT and MR enterography with oral 2% barium sulfate and IV gadolinium in known CD patients and found similar findings in majority of patients. SBFT showed additional strictures and fistulae in four patients while MRE showed additional information regarding active inflammation in stricture areas like wall enhancement, vasa recta changes and lymphadenopathy in 8 patients.

Detection of proximal ileal disease is crucial because it is inaccessible on ileocolonoscopy. Ochsenkuhn and colleagues (163) reported superiority of MRE over SBE of MRE for this purpose as well. Using features including wall thickness, contrast enhancement and detection of stenosis, they diagnosed proximal ileal disease in 22 of 25 patients whereas SBE was only able to reveal disease in 4 of these patients.

A year later, Albert et al (164) not only compared MRI with double contrast fluoroscopy and capsule endoscopy at the same time. Small bowel Crohn's disease was diagnosed in 78% (MRE), 33% (Barium) and 93% (WCE) but again MRI was superior in identifying transmural CD and extraluminal lesions and exclusion of strictures.

Lee and colleagues (165) compared the accuracy of MRE, CTE and SBFT while using ileocolonoscopy as reference standard for small bowel inflammation and imaging studies and surgery and physical examination for extraenteric complications. They

found 100% sensitivity for both MRE and CTE in comparison to just 37% for SBFT for detection of extra enteric complications. Therefore, they presented MRE as effective and radiation free diagnostic tool for disease assessment in IBD.

In summary, MR enteroclysis and enterography provide complementary information to endoscopy and provide radiation free additional information about extra intestinal complications.

1.3.3 MAGNETIC RESONANCE COLONOGRAPHY

1.3.3.1 Background

Magnetic resonance imaging Colonography (MRC) has evolved quickly since the first main description in 1997. Luboldt et al (166) performed the first MRC in three patients, one of them had comparative DCBE and the others also underwent colonoscopy as well. MRC was able to demonstrate the colonic tumour and polyps. Luboldt used 1.5-2 L of water mixed with gadolinium- diethylenetriaminepentaacetic acid (Gd-DTPA) to distend the patient's colon together with IV Gd-DTPA. MRI (pre and post contrast) and MRC was performed in prone and supine positions. The authors suggest MRC could be an accurate, minimally invasive and cost effective modality for polyp screening and colonic tumour staging.

Since then, although some are developing the role of MRC in colonic cancer detection, the focus for the technique is increasingly for use in IBD (167-169). Studies have shown a good correlation between MRI findings and alternate modalities (including conventional radiography, CT, endoscopy, and surgery) as well as clinical disease activity grading. MRC shows considerable promise as a less invasive alternative to colonoscopy in evaluating the location, severity and activity of colonic IBD.

There are two methods to perform MRC depending on the nature of fluid used to fill the colon; the bright lumen or dark lumen technique.

1.3.3.2 Bright lumen MRC

Distention of bowel with fluid labeled with an agent with strong T1- weighted signal is referred as “bright lumen”, and the method used by Lubolt in 1997 (166). Typically, a gadolinium/water mixture (5mmol/L) is applied rectally after conventional bowel cleansing resulting in high signal on both T1 and T2 sequences. Bowel distension can be monitored in real time using a fast T2-weighted TrueFisp sequences (170). 1.5-2.5L of fluid is usually used to fill the whole colon. When the target is colorectal neoplasia, two data sets are collected (one in prone and other in supine position) to move for the residual air pockets, which can reduce accuracy. Colorectal lesions appear as solid filling defects, which require differentiation from air bubbles and stool residue.

Changing the patient position during the procedure however does prolonged the procedure and may precipitate escape of contrast into small bowel reducing colonic distension and diagnostic quality (168).

The luminal high signal can impair differentiation between lumen and colonic wall and mural enhancement is less well appreciated. Detection of abscesses may be improved with the technique which may be difficult to distinguish from water filled bowel loops when using a dark lumen method (171).

1.3.3.3 Dark lumen MRC

Although the dark lumen technique is a recent development, it has largely replaced the bright lumen technique as the methods of choice for MRC (14, 168, 171). The dark lumen is achieved by filling the colon with water, air or carbon dioxide. One advantage of dark lumen is that mural contrast enhancement is readily appreciated. As water itself is biphasic, it gives low signal on T1- weighted images and high signal intensity of T2-weighted images.

As well as the advantage in terms of clearer appreciation of the contrast enhancement, dark lumen MRC facilitates direct analysis of the bowel wall and appreciation of inflammatory changes such as increased contrast uptake and bowel wall thickness, sub-mucosal edema, mesenteric fat stranding, mesenteric hyper vascularity and fibro-fatty proliferation (124). It is also helpful in diagnosing polyps and bowel masses.

Because residual air has a similar T1 signal to water, the risk of false positive diagnosis is reduced compared to the bright lumen technique and there is no need to change patient position during the scan (172) which saves time .

Typical protocol

Typical MRC protocols require bowel preparation to cleanse the bowel before the imaging. Akin to imaging the small bowel, most of colonic segments are physiologically collapsed so cannot be assessed properly before the colon is distended by administration of a distending media via rectal catheter. The patient is usually examined in prone position and two surface array coils are used to obtain homogenous and complete MR signal reception. The administration of anti peristaltic agents helps to reduce motion artifacts.

For optimal evaluation of inflammatory lesions in IBD, imaging should include both T2 and T1 weighted sequences.

A true –FISP in the coronal plane is acquired to confirm sufficient and homogenous bowel filling. The colon wall is well seen on this sequence due to the contrast difference between the hypointense wall and the bright lumen.

Half-Fourier acquisition single-shot turbo-spin echo (HASTE) T2 weighted sequences are then acquired in the axial and coronal plane after administration of IV spasmolytic.

These -T2 images depict mural edema, pericolonic inflammatory changes and mesenteric free fluid (Figure 1).



Figure 1: HASTE – T2 weighted sequence on Dark lumen MRC

Finally, T1 – weighted images (pre and post contrast) are acquired which also help assess morphological features, but in addition provide information on disease activity-in general the degree of enhancement reflects the severity of inflammation.

Typically, a fat suppressed fast 3D gradient sequence such as 3D-FLASH or an interpolated sequence such as VIBE (volumetric interpolated breath hold examination) should be acquired 70-75 s after contrast (gadolinium) injection (Figure 2).

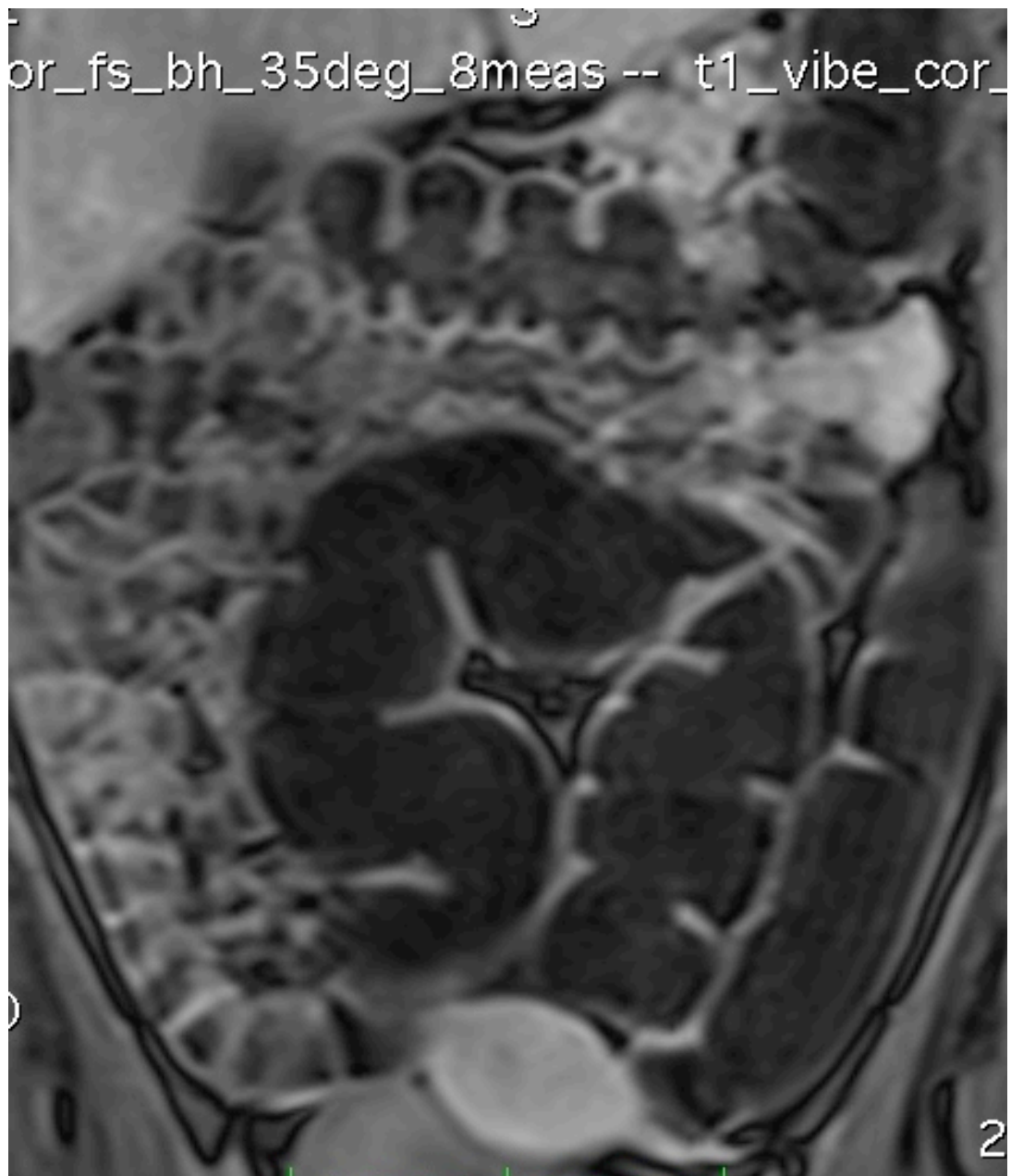


Figure 2: T1 weighted images on Dark lumen MRC

1.3.3.4 Enteric Findings in IBD

- Increase wall thickness- Shortening of colonic haustral folds- in moderate to severe disease activity although it may be a normal feature in descending and sigmoid colon in some healthy individuals.

- Mural hyper enhancement- significant increased enhancement after IV contrast may correlate with the severity of active inflammation.
- Mural edema- it is seen as increased signal of colonic wall on T2-weighted images.
- Fibrostenotic lesions of bowel wall- thickened wall with low level contrast enhancement, with or without luminal pre stenotic dilatation.

1.3.3.5 Mesenteric findings

- Abscess – fluid or heterogeneous content with contrast enhancement of the wall
- Lymphadenopathy
- Fistulae and sinuses- linear hyperenhancing tract on post contrast T1-weighted sequence and hyper signal on T2 due to the fluid content (Figure3-5).

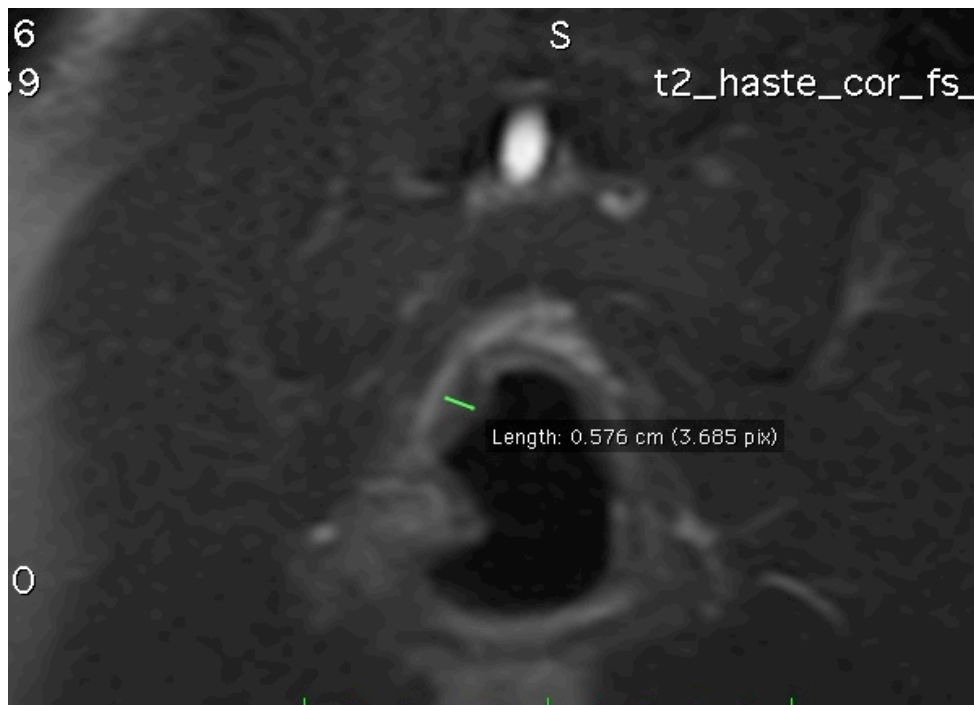


Figure 3: Increased wall thickness of rectum and increase perimural T2 Signals

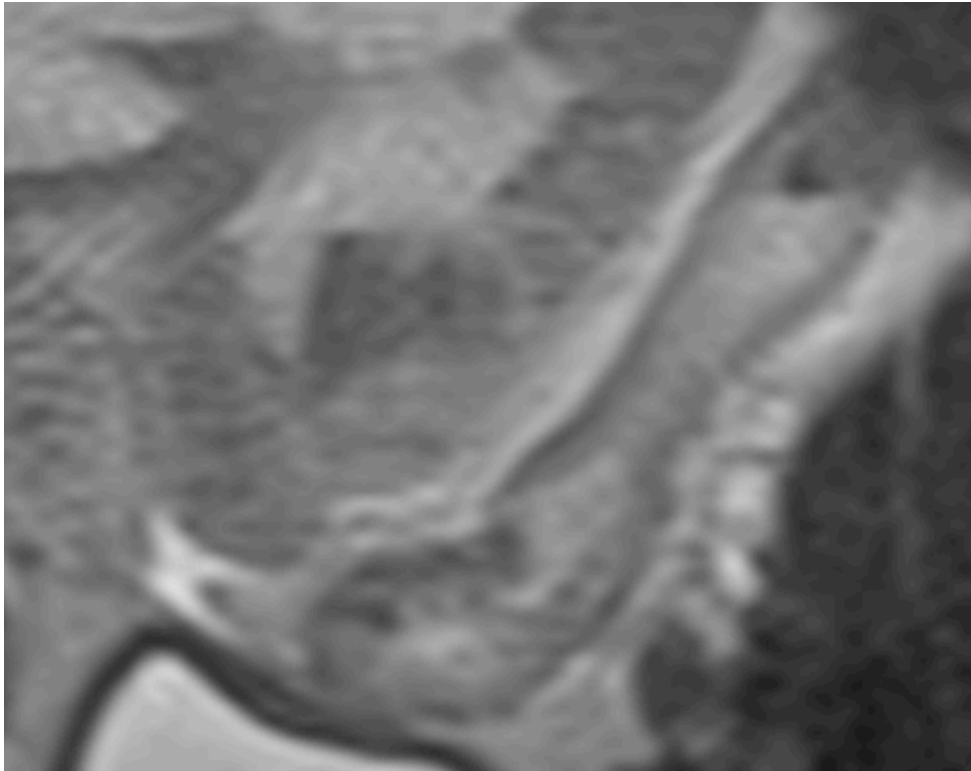


Figure 4: Loss of haustral folds in diseased Sigmoid colon



Figure 5: Mural hyper enhancement of rectum

1.3.3.6 Review of literature pertaining to MRC in IBD

Several studies have compared the diagnostic accuracy of MRC with CC for detection and assessment of IBD. In one such study Scheryer et al (171) performed MRC and CC on same day by using the bright lumen method and graded colonic segments and terminal ileum by a three-point scale of inflammation. MRC only achieved 58.8% sensitivity for UC and 31.6% for CD on segmental bases. The authors did not recommend the use of bright lumen MRC for routine assessment of IBD as detection of early inflammation in cases of CD and even severe inflammation in UC was missed on MRC. Ajaj et al (14) first employed the dark lumen technique for the detection of colorectal neoplasia. MRC achieved sensitivity of 93% and specificity of 100% in comparison to CC for diagnosis of colorectal masses and inflammatory lesion by using dark lumen method.

Two years later (15), the same group proposed a diagnostic score of disease activity based on bowel wall contrast enhancement, bowel wall thickness, presence of perifocal lymph nodes and loss of haustral folds (table 14) In comparison to endoscopic biopsies MRC achieved sensitivity of 87% and specificity of 100% for detecting inflammation.

Contrast uptake	Wall thickness	Haustral Folds	Peri focal LN
0- no uptake	0= no thickening	0= no loss of folds	0= no LN
1= < 25%	1=<25% increase	1=<25% loss	1=1-4 LN
2=25-50%	2=25-50% increase	2= 25-50% loss	2= 5-10 LN
3=>50%	3=>50% increase	3= > 50% loss	3= >10 LN
Slight inflammation = ≤ 4 points	Moderate inflammation= 5-8 points	Severe inflammation= >8points	

Table 14: MRC Inflammation score by Ajaj et al (15)

The ability of MRC to accurately detect extra-luminal complications has also been reported, often leading to a change in therapeutic strategy (125).

As with any MR technique some patients are unable to undergo the test due to claustrophobia and as will be explored later in this thesis, for some holding water and breath holds are difficult parts (173, 174).

1.3.3.6.1 MRC without bowel preparation

Although MRC is often performed after full laxation, it is known bowel preparation is often poorly tolerated: 75% of patient under going bowel preparation express symptoms ranging from “feeling unwell” to “inability to sleep” (175).

“Fecal tagging” is a concept introduced to avoid bowel cleansing prior to radiological colonic imaging. It involves ingestion of contrast compounds such as barium sulfate, ferumoxil solution containing 5% gastrograffin, 1% barium and 0.2% locust bean gum added to regular meals 36 hours prior to examination in order to modify the signal

intensity of colonic content to match that of the rectal enema. In affect, the fecal material becomes “virtually invisible”(176).

Most of the literature pertaining to non-laxative MRC pertains to the use of the technique in detecting colorectal neoplasia.

Lauenstein and colleagues (177) applied a dark lumen technique after fecal tagging with barium sulfate in patients with colonic symptoms and used colonoscopy as reference standard. Reported sensitivity was 89.3% for detection of polyps and carcinoma. In another study, Goehde et al found poorly tagged stool signal in 18% of patients.

Although, overall sensitivity of 100% for detection of polyps larger than 2 cm while it was 40% for polyps between 10-19mm in comparison to conventional CC. Interestingly however, patients rated the ingestion of large amount of barium sulfate (150 ml at each 6 meals before procedure) as worse than bowel preparation (178).

Florie and colleagues (179) used limited bowel preparation with lactulose and fecal tagging with gadolinium and compared patient experience and preference with conventional CC. Patients found MRC with limited bowel preparation less burdensome ($p < 0.001$) and less painful ($p < 0.001$) than CC. Overall patient preference was higher for MRC immediately and even after 5 weeks. Similar higher acceptance for MRC with fecal tagging is found in other studies (124, 180).

The role of MRC with fecal tagging in detection of inflammatory bowel disease activity has been evaluated but with disappointing results. One study reported just 32% sensitivity and 88% specificity for detection of inflamed segment in comparison to conventional CC (181). Difficulty in identification of inflammatory changes, particularly in establishing precise measurements of wall thickness and obscuration of

the presence of ulceration perhaps make the technique less suitable method for adequate assessment of IBD.

An alternative approach is to reduce stool signal by increasing its water content (so called “fecal cracking”) Ajaj et al (182) used the oral stool softener lactulose and rectal stool softener docusate sodium (DS) for this purpose. Stool signal intensity was compared in patients without any stool softeners, after use of oral lactulose only, after rectal ducosate sodium only and the combination of oral lactulose and rectal DS. The lowest stool signal intensity was seen after combination of oral and rectal softeners but clinical usefulness of this method still needs to be assessed.

As discussed above basic T1 and T2 weighted sequences are the mainstay of enteric imaging using MRI. There has however been some work investigating the use of novel sequences such as diffusion weighted imaging. The signal from diffusion weighted images is dependent on the movement of water in the extra-cellular tissues. It was seen intuitive that the inflammatory component of IBD would affect the signal in diffusion weighted images (either restricting diffusion due to increased inflammatory cells, or facilitating water movement due to tissue edema). Oussalah et al (183) performed diffusion weighed imaging (DWI) during MRC without bowel cleansing in patients with known IBD. Disease activity was assessed using an MR score based on DWI hyperintensity, Gadolinium enhancement pattern after IV administration, bowel wall thickening, parietal edema and presence of ulcers. The MR score achieved better accuracy for detection of inflammation in UC than CD, and demonstrated significant correlation with diagnostic scores such as the modified Baron score and Walmsley index. Continuous and diffuse colonic inflammation in UC was better detected using diffusion – weighted MR as compared to the segmental involvement of CD. Bowel wall thickness was the best marker of CD, likely reflecting trans mural inflammation. The

lack of bowel preparation and relative short acquisition time of the procedure improved patient compliance (Figure 6).



Figure 6: Diffusion weighted imaging during MRC

1.3.4 COMBINED ASSESSMENT OF SMALL AND LARGE BOWEL

Given the potential of CD to affect anywhere in the GI tract, an MRI techniques that can assess both the small bowel and large bowel at the same time would be intuitively of interest. Simplistically it is possible to perform both MRE and MRC at the same time. This technique has been used with some promising results. For example Low and colleagues (184) used 2% barium orally and rectal water in patients with known IBD. They compared T2 weighted breath- hold single- shot fast spin –echo (SE) and

gadolinium enhanced spoiled gradient-echo (GRE) MR imaging with endoscopy, barium study and surgery. GRE MR imaging was better in depicting disease extent and severity in comparison to SE MR imaging with per patient sensitivity of 100% vs. 60%, per segment sensitivity of 89% vs. 52% with overall disease detection in 93% patients in comparison of 43% patients respectively.

Ajaj et al (185) compared MRI findings in two groups of patients. One group had MRE with 0.2% locust bean gum and 2.5% mannitol while the other group had an additional rectal water enema. They found better diagnostic accuracy in terminal ileum and colon in those receiving the enema due to better distension of bowel, although noted the induced discomfort of the combined technique to patients. Similarly Scheryer et al also found improved diagnostic value with combined MR Enteroclysis and MRC approach (186). They used T2 weighted and contrast enhanced T1 weighted sequences as an integrative protocol and colonoscopy as reference standard.

Rimola and colleagues in two consecutive studies use the combine technique to derive and validate an MRI index of disease activity. In first study (16), they applied the combined technique by using 1500 ml of iso-osmotic PEG and electrolyte solution for distention of the small bowel and a water enema (1-2L) via a rectal catheter to fill the colon. Intravenous gadolinium was administered. 50 known IBD patients had ileocolonoscopy and MRI. The CDEIS was used to assess endoscopic activity and they proposed a magnetic resonance index of activity (MRIA) based on wall thickness, post contrast wall signal intensity, relative contrast enhancement, presence of mural edema, ulcers, pseudopolyps and lymph node enlargement.

$$\text{MRIA index} = 1.5 \times \text{wall thickness} + 0.02 \times \text{RCE} + 5 \times \text{edema} + 10 \times \text{ulcers}$$

There was significant correlation between CDEIS and MRIA ($r=0.82$, $p<0.001$) and the authors reported high accuracy of MRIA for detection of disease activity (ROC 0.891, sensitivity 0.81 and specificity 0.89), and detection of ulcerated lesions (ROC 0.978, sensitivity 0.95, specificity 0.91) in colon and terminal ileum. The global MRIA also showed significant correlation with CDEIS ($r=0.78$, $p<0.001$), Harvey – Bradshaw index ($r=0.56$, $p<0.001$) and CRP ($r=0.53$, $p<0.001$).

In second study from the group (187), same quantitative Magnetic Resonance index (MaRIA = $1.5 \times \text{wall thickness} + 0.02 \times \text{RCE} + 5 \times \text{edema} + 10 \times \text{ulceration}$) was compared with CDEIS while endoscopy disease activity was also classified as absent, mild (inflammation without ulcers) and severe (presence of ulceration). Wall thickness, relative contrast enhancement (RCE), presence of edema and ulcers were validated as independent predictors of disease severity as in the previous study. MaRIA correlated with CDEIS ($r=0.798$, $p<0.001$ per segment and $r=0.87$, $p<0.001$ per patient). Therefore, the authors proposed the use of this index to categorize disease severity and to monitor response to therapeutic interventions.

Hyun et al (188) also reported comparable results between endoscopy (ileocolonoscopy & double-balloon endoscopy) and magnetic resonance enterocolonography (MREC). Sensitivity of MREC for detection of deep mucosal lesions was 88.2 %, for all CD lesions was 61.8% and for stenosis was 71.4% for colon and 100, 85.7 & 100% for small bowel respectively.

1.3.5 REVIEW OF LITERATURE – REGARDING USE OF MRI FOR DISEASE ASSESSMENT OF IBD

Different MRI parameters have been used as criteria for disease detection and evaluation such as wall thickness, contrast enhancement, lymphadenopathy, comb sign, loss of haustrations and detection of stenosis and the summary of some of the studies and criteria used is described in Table 15.

Study Year	Magnetic field	Luminal contrast	IV contrast	Coil	Criteria
Low et al(157) 2000	1.5 T	1350 mL 2% barium-oral, 0.5-1 L water - rectal	0.1 mmol/kg Gadopentetate dimeglumine	Body	Wall thickness Enhancement
Rieber et al (161) 2000	1.5 T	Enteroclysis	0.1 mmol/kg Gadopentetate dimeglumine	Surface	Wall thickness Stenosis
Schunk et al (149) 2000	1.0T	2.5% mannitol	0.1 mmol/kg Gadopentetate dimeglumine	Body	Enhancement
Koh et al (158) 2001	1.0 T	600 mL water – oral	0.1 mmol/kg Gadopentetate dimeglumine	NA	Enhancement Wall thickness lymph - adenopathy Comb sign

Miao et al (150) 2002	1.0T	600 mL water- oral	0.1 mmol/kg Gadopentetate dimeglumine	NA	Enhancement Wall thickness Lymph - adenopathy Comb sign
Laghi et al (151) 2003	1.5T	10mL/kg polyethylene glycol – oral	0.1 mmol/kg Gadopentetate dimeglumine	Surface	Enhancement Wall thickness
Ochsenkuhn et al (163) 2004	1.5T	400mL barium, 1.5-2L ferristerne (enteroclysis)	0.1 mmol/kg Gadopentetate dimeglumine	NA	Enhancement Wall thickness Stenosis
Ajaj et al (185) 2005	1.5T	3L polyethylene glycol –oral 1.5-2L water – rectal	0.2 mmol/kg Gadopentetate dimeglumine	Surface	Enhancement Wall thickness Haustration Lymph - adenopathy
Schreyer et al (189) 2005	1.5T	Polyethylene glycol –oral 1.5 L Gadopentetate dimeglumine in water (5mmol/L)	0.1 mmol/kg Gadopentetate dimeglumine	Surface	Enhancement Wall thickness Comb sign Lymph - adenopathy

Schreyer et al (186) 2005	1.5T	2L water-oral 700mL 0.9% NaCl rectal	0.2mmol/kg Gadopentetate dimeglumine	Surface	Enhancement Wall thickness Comb sign Lymph - adenopathy Stenosis
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Table 15: MRI imaging features in inflammatory bowel disease (190)

1.3.5.1 Accuracy of MRI in diagnosis of IBD

Studies have reported overall sensitivity of 78% (95% CI 67-84%) and specificity of 85% (95% CI 76-90%) on per patient basis for diagnosis in patients with suspected CD in comparison to clinical, endoscopic and SBE findings as summarized in Table 16

Study	Patients *	Population	Reference standard	Location evaluated	Sensitivity (%)	Specificity (%)
Albert et al (164)	25/14	Adults	Ileo-Colonoscopy SBCE	Small bowel	77	80
Pilleul et al (152)	15/6	Children	Ileo-Colonoscopy	Small & large bowel	83	100
Borthne et al (143)	20/NA	Children	Colonoscopy	Small & large bowel	82	100
Horsthuis et al (159)	33/15	Children	Endoscopy (ileo-colonoscopy gastroscopy) Enteroclysis, Clinic	Small & large bowel	61-91 (2 observers)	60-90 (2 observers)

*No of patients included / No of patients confirmed

Table 16: Accuracy of MRI in diagnosis of IBD on a per patient basis (191)

1.3.5.1 Assessment of disease extent

Studies have reported that MRI has sensitivity of 74% (95% CI 68-80%) and specificity of 91% (95% CI 86-95%) for small bowel extent (table 17).

Study	Patient with CD total /active	Population	Reference standard	Location evaluated	Sensitivity %	Specificity %
Low et al (184)	28/25	Adults	Barium studies, High resolution endoscopy Surgery	Small & large bowel	86	NA
Pascu et al (110)	37/NA	Adults	Ileocolonoscopy	TI & colon	38	90
Albert et al (164)	52/30	Adults	Capsule endoscopy	Small bowel	85	100
Tillack et al (145)	19/18	Adults	Capsule endoscopy	Small bowel	78	91
Fiorino et al (148)	44/28	Adults	Ileocolonoscopy Surgery	Small bowel and colon	88	88

Table 17: Accuracy of MRI in the assessment of disease extent in IBD (191)

1.3.5.1 Assessment of disease activity

Overall sensitivity of MRI for the assessment of disease activity on per patient is 80% (95% CI 77-83%) and specificity 82% (95% CI 78-85%) whereas on per segment basis it is 70% (95% CI 67-73%) and 89% (95% CI 93-96%) respectively. Below is the summary of some of these studies using different reference standard.

Study	Patients total /active	Reference standard	Location	Sensitivity %	Specificity %
Low et al (157)	26/NA segment 193/65	Endoscopy Enteroclysis Barium enema Surgery	Small and large bowel	80-85	91
Koh et al (158)	30/7 segment 124/30	Ileo- colonoscopy	TI and colon	59 91	93 71
Miao et al (150)	30/23	Ileo- colonoscopy	TI and colon	87	71
Neurath et al (192)	51/51 segment 139/42	Ileo- colonoscopy	TI and colon	67	93
Ochsenkuhn et al (163)	25/18	Ileo- colonoscopy	TI	88	85
Pilleul et al (152)	62/23	Ileo- colonoscopy	TI and colon	78	46
Schreyer et al (186)	30/29 segment 161/49	Ileo- colonoscopy	TI and colon	55	98
Florie et al (141)	31/21	Ileo- colonoscopy	TI and colon	93	55
Horsthuis et al (142)	20/16	Ileo- colonoscopy	TI and colon	100	100

Lee et al (165)	30/18	Ileo- colonoscopy	TI	83	100
Rimola et al (16)	50/3 segment 218/83	Ileo- colonoscopy	TI and colon	81	89
Siddiki et al (147)	30/21	Ileo- colonoscopy	TI	91	67
Fiorino et al (148)	44/28	Ileo- colonoscopy Surgery	Small bowel Colon	81-90	91-95
Oussalah et al (183)	61/NA segment 221/NA	Ileo- colonoscopy	TI and colon	58	84
Hyun et al (188)	30/20 230/64	Ileo- colonoscopy Cap endoscopy	Small bowel Colon	86 62	93 95
Rimola et al (187)	48/29 258/115	Ileo- colonoscopy	Small bowel Colon	87	87

Table 18: Accuracy of MRI in the assessment of disease activity in IBD (191)

1.1.1.1 Assessment of disease severity

For the purpose of assessment of disease severity different MRI parameters and indices have been compared with endoscopy (ileocolonoscopy, Capsule endoscopy and double balloon enteroscopy) (table 19).

Study	Patient with CD total /active	Population	Reference standard	Location evaluated	Results
Pascu et al (110)	37/NA	Adults	Ileocolonoscopy	TI Colon	Correlation between MRI index and endoscopy activity index $r=0.344, p=0.007$
Florie et al (141)	31/21 segments 141/NA	Adults	Ileocolonoscopy	TI Colon	Correlation between MRI and endoscopy severity 0.59 (observer 1)- 0.53 (observer 2) $p<0.001$
Schreyer et al (186)	30/29	Adults	Ileocolonoscopy	TI Colon	Distinction between mild, moderate and severe disease. Sensitivity 69%, Specificity 99%
Horsthuis et al (142)	20/15	Adults	Ileocolonoscopy	TI Colon	Lack of correlation between MRI severity and endoscopic severity $r=0.4, p=0.09$
Tillack et al (145)	19/18 segments 40/NA	Adults	Capsule endoscopy	Small bowel	Distinction between mild, moderate and severe Sensitivity 58%, Specificity 77%

Rimola et al (16)	29/48 segments 115/258	Adults	Ileocolonoscopy	TI Colon	Distinction between mild, moderate and severe Sensitivity 91%, Specificity 95%
Oussalah et al (183)	61/NA segments 211/NA	Adults	Ileocolonoscopy	TI Colon	Correlation between MRI index and endoscopic severity index $r=0.659, p<0.001$
Rimola et al (187)	48/NA segments 158/115	Adults	Ileocolonoscopy	TI Colon	Distinction between mild, moderate and severe Sensitivity 92%, Specificity 92% Correlation between MRI index and endoscopic severity index $r=0.84, p<0.001$
Hyun et al (188)	30/20	Adults	Ileocolonoscopy Double balloon enteroscopy	Small bowel Colon	Correlation between MRI index and endoscopy severity index $r=0.85, p<0.001$

Table 19: Efficacy of MRI in the assessment of disease severity in IBD (191)

1.3.5.2 Assessment of complications in IBD

In comparison to endoscopy, barium radiology, US, CT and surgery, MRI has shown sensitivity of 40 -100% for detection of intra abdominal fistulae and sensitivity of 86% (95% CI 79-91%) specificity of 93% (95% CI 88-97%) for the detection of abscesses (table 20).

Study	Patients with CD	Reference standard	Complications (n)	Sensitivity (%)	Specificity (%)
Magnano et al (140)	22	Endoscopy	Stenosis (8) Abscess (1)	87 NA	92 NA
Horsthuis et al (142)	47	Endoscopy	Stenosis (7)	86	85
Pilleul et al (152)	47	US Surgery	Stenosis (8) Fistula (9)	100 100	100 100
Florie et al (141)	31	Endoscopy	Stenosis, fistula, abscess (8)	75	91
Maccioni et al (139)	59	Endoscopy CT, US Barium radiology Surgery	Stenosis (22) Fistula (9) Abscess (4)	91 78 86	100 100 93
Negaard et al (160)	35	Endoscopy	Stenosis (9)	86	93
Tillack et al (145)	19 (52 segments)	Capsule endoscopy Endoscopy	Stenosis (22)	82	93
Martinez et al (155)	30	Endoscopy Barium radiology	Fistula (17)	71	92

		Surgery			
Lee et al (165)	30	Endoscopy	Fistula (11)	100	100
		Barium radiology	Abscess (5)	100	100
		Surgery			
Fiorino et al (148)	44	Endoscopy	Stenosis (14)	92	90
		Surgery	Fistula (5)	40	94

Table 20: Accuracy of MRI in the assessment of complications in IBD (191).

In summary, MRC appears to be a useful examination that is complementary to colonoscopy in assessing the colon. Indeed use is increasing where the whole colon cannot be explored using colonoscopy for technical reasons, patient intolerance, stenosis, or due to a perceived higher risk of perforation. The ability of MRC to detect colonic inflammation is one of the central themes of this thesis, along side its ability to monitor therapeutic responses and prognosticate in severe colitis.

2 SECTION TWO: CURRENT USE AND DIAGNOSTIC IMPACT OF ENTERIC MRI

2.1 USE OF SMALL BOWEL IMAGING FOR THE DIAGNOSIS AND STAGING OF CROHN'S DISEASE – A SURVEY OF CURRENT UK PRACTICE

2.1.1 INTRODUCTION

As discussed in Chapter 1, despite advances in technology, the small bowel remains relatively inaccessible to conventional endoscopic techniques and radiological imaging plays a major role in the assessment and diagnosis of both luminal small bowel disease, and extra-enteric complications.

Although barium fluoroscopy and CT remain the conventional tests, both impart a significant radiation dose to patients (193, 194), which is of major importance given the relatively younger patient population afflicted by Crohn's disease (195). The recently published European evidenced based consensus on the diagnosis and management of Crohn's disease (196) states "the radiation burden from fluoroscopy and CT is considerable so alternatives such as ultrasound and MRI should be considered when possible." Although advocates of ultrasound and particularly MRI suggest they may be the ideal "one stop shop" in Crohn's imaging, evaluating luminal, mural and extra-mural disease, there is a relatively small evidence base upon which to rationalise the implementation of new imaging technologies within the NHS and it is unclear to what extent they have disseminated into routine UK clinical practice. The purpose of the

survey was therefore to assess the current utilisation of individual small bowel imaging investigations for Crohn's disease within NHS radiological practice, and to gauge current gastroenterological referral patterns

2.1.2 MATERIALS AND METHODS

Two similar questionnaires were devised for distribution to UK NHS departments of Radiology and Gastroenterology (appendix A and B). The questionnaires included various clinical scenarios relevant to the imaging diagnosis and management of Crohn's disease, including first diagnosis of small bowel disease, small bowel staging in known disease, assessment of suspected extra luminal complications and possible obstruction, and imaging of suspect disease flare. The questionnaires were devised in collaboration with local gastroenterologists (Stuart Bloom and Sara McCartney) and they approved clinical definitions used.

Additional information captured by the radiological questionnaire included the type of hospital (teaching, district general or other) and the specific use of oral contrast agent if small bowel MRI was being performed. Space for additional comment was included on the questionnaires. The gastroenterological questionnaire also included colonoscopy as an investigatory option given conventional endoscopic technique is in the main at the disposal of clinicians rather than radiologists. The imaging options available to gastroenterologist were also simplified (e.g. MRI techniques not subdivided into enterography and enteroclysis) to improve particularly respondent compliance and reduce any potential confusion with imaging terminology.

For each question, it was permissible to tick more than one imaging test option if more than one test was routinely concurrently performed. Importantly, in each clinical

scenario, patients were sub stratified according to age to capture data on any perceived barrier to use of those tests utilising ionising radiation in younger cohorts.

2.1.2.1 Questionnaire Distribution

A list of UK departments of Radiology was obtained from the Royal College of Radiologists with approval from the Audit Committee. A list of Gastroenterology departments was obtained from the British Society of Gastroenterologists. In January 2008, 240 questionnaires were sent out by Rehana Hafeez, Rebecca Greenhalgh and Janaki Rajan to the Clinical directors of the departments of Radiology and 254 questionnaires were sent to Clinical directors of the departments of Gastroenterology with a covering letter asking the questionnaire be given to the most appropriate clinician in the department to fill out. A stamped addressed envelope was included for return of the questionnaires. The questionnaires were sent out a second time 2 months later to departments that had not replied. A copy of the questionnaire was also posted on the British Society of Gastrointestinal and Abdominal Radiologists website (www.bsgar.org) and members invited to participate if their hospital had not done so already.

2.1.3 RESULTS

The final return rates for Radiology departments were 27% (63 replies from 20 teaching hospital and 43 DGHs) and 29% (73 replies) for departments of Gastroenterology. 17 replies were from radiology and gastroenterology departments from the same hospital.

2.1.3.1 Tests offered and overall frequency of use

55 (90%) of 63 radiology departments routinely performed Barium studies. Barium follow through (BaFT) was the most commonly performed procedure with an average of 15.4 examinations per department per month (range 1-50), of which 67% were for

suspected diagnosis and 33% for disease follow-up. Twenty two (35%) radiology departments offered barium enteroclysis (BE) (59% for suspected disease).

Forty four (72%) departments performed CT with oral contrast (CTO) with on average 5.1 scans per department per month (range 1- 20), among these 51% for suspected disease while 49% for disease follow-up. CT enteroclysis (CTE) was performed in 7 (11% of total departments) centres (5 of which were teaching hospitals).

46% (29) of radiology departments offered small bowel ultrasound (SbUS), on average 7.5 per department per month (range 1-30), 61% of these for suspected disease and 39% for follow up. 13 out of these 29 were teaching hospitals

Just 38% (24) of departments who replied, offered any small bowel MRI service (MRIO), on average 5.04 per department per month (range 1 – 20), of which 60% were performed for disease follow-up. Of those stating their preference of oral contrast, Kleen prep and mannitol were preferred equally (21% each), locust bean gum/mannitol solution by 12.5% and Gastrograffin by 9 %. Seven centres (6 of which were teaching hospitals) offered MR Enteroclysis (MRIE), performing on average 78 per month between them, the majority (62%) for disease follow-up.

11 (6 teaching hospitals) performed between them on average 83 Capsule endoscopies (Cap E) per month, 64% for suspected disease.

2.1.3.2 Use of tests according to indications- Radiologists

For imaging of the small bowel in newly diagnosed Crohn's disease, barium follow through was the most commonly used investigation across all age groups (Figure 7), for example 34 (54%) radiology departments used it in those aged <20 years and 43 (68%) for patients above the age of 61. Small bowel ultrasound (SbUS) and MR were used

more frequently in patients <40 years old, but only then by 18 (29%) and 17 (27%) of departments respectively. CT was infrequently used in patients below 40 and only by 10 (16%) of departments even in those over 60 for this indication. Sixty percent of departments use a single imaging modality only, but 40% suggest they offer more than one test in combination.

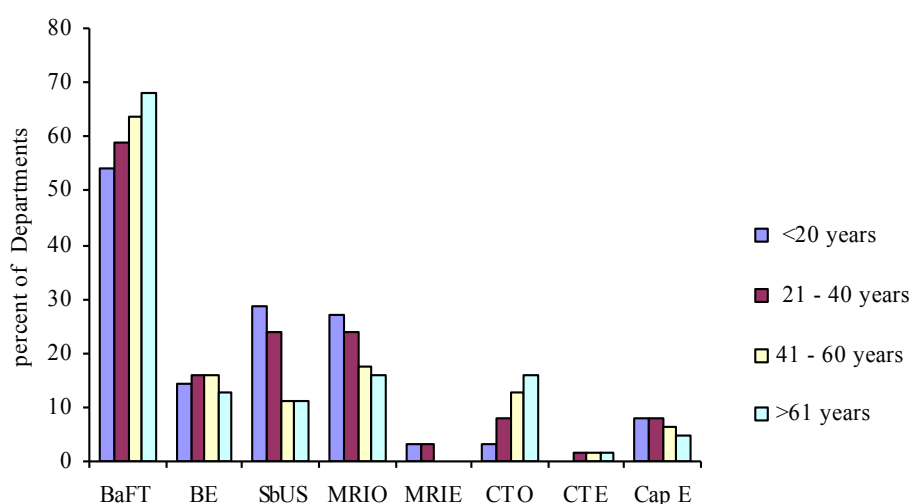


Figure 7: First line investigation performed by Radiologists in newly diagnosed Crohn's disease patients. Barium follow through (BaFT) is most commonly used while small bowel USS (SbUS) and MRIO relatively more frequently used in younger patients.

Similarly, in patients with a suspected but unknown diagnosis of small bowel Crohn's disease, barium follow through was also the most commonly used investigation regardless of whether there is high or low clinical suspicion of disease (42 [67%] of departments averaged across the age groups) (Figure 8).

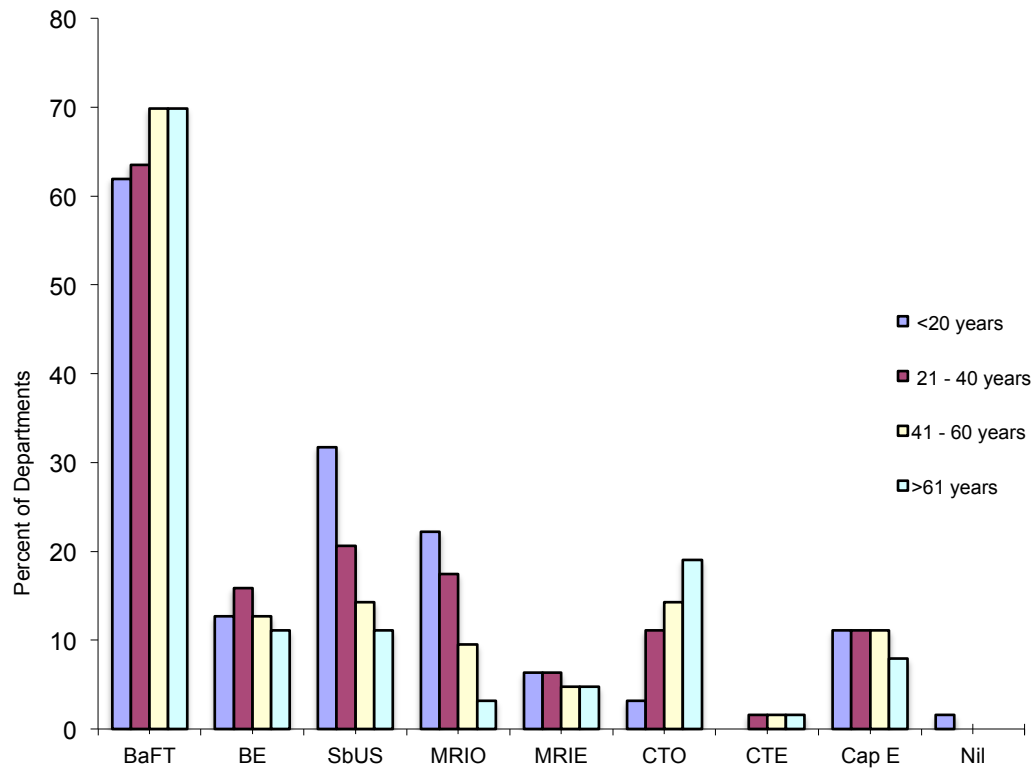


Figure 8: Investigations used in patients with high clinical suspicion of Crohn's disease.

Standard barium tests are performed more frequently than cross sectional imaging.

Interestingly however, in those with a low clinical suspicion, SbUS was used relatively commonly, particularly in those aged below 20 (28 [44%] of departments) (Figure 9).

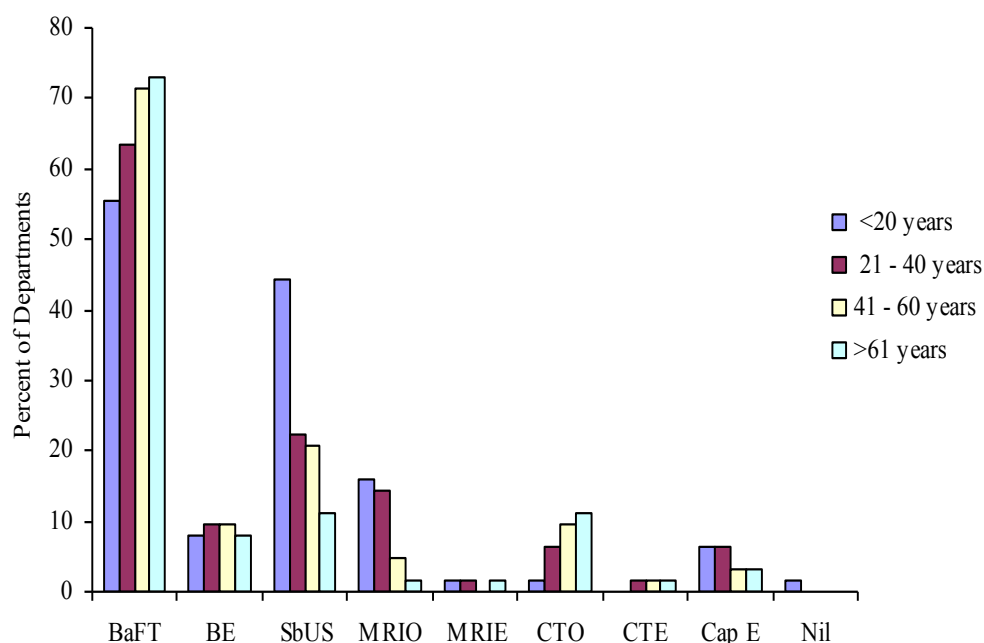


Figure 9: Investigations in patients with a low clinical suspicion of Crohn's disease.

BaFT is most commonly used investigation in all age groups while SbUS is used relatively commonly in patients younger than 20 years.

Once again CT was infrequently used (by a maximum of 12 (19%) of departments in those aged over 61 years and with a high clinic suspicion of disease, and MRI was most frequently used in those age less than 20 with a high clinical suspicion (14 [22%] of departments).

Conversely when extra-luminal complications (such as fistula or abscess) were suspected, CT became the most commonly performed (for example by 34 [54%] and 46

[73%] departments for those aged less than 20 and > 60 years respectively). SbUS and MR studies were most commonly used in younger patients, but even then less than CT (Figure 10).

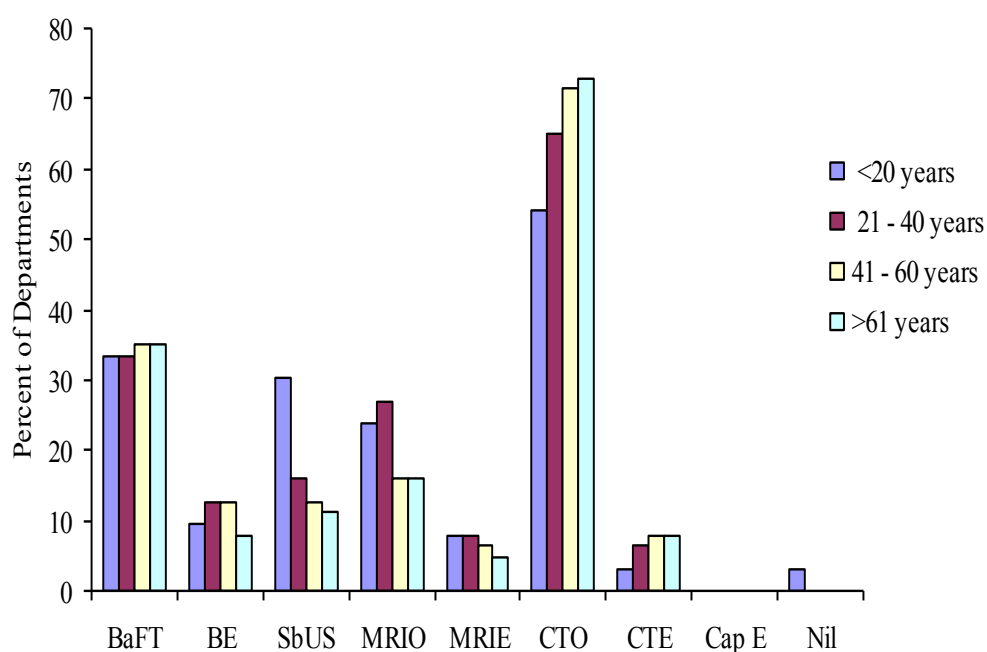


Figure 10: Investigations used for patient with suspected extra luminal complications.

CT is the preferred investigation in all age groups followed by BaFT although

SbUS and MR are used with increased frequency in younger patients.

In outpatients with suspected obstruction, BaFT and CTO were most frequently used (36 [57%] and 29 [46%] of departments averaged across the age groups (Figure 11).

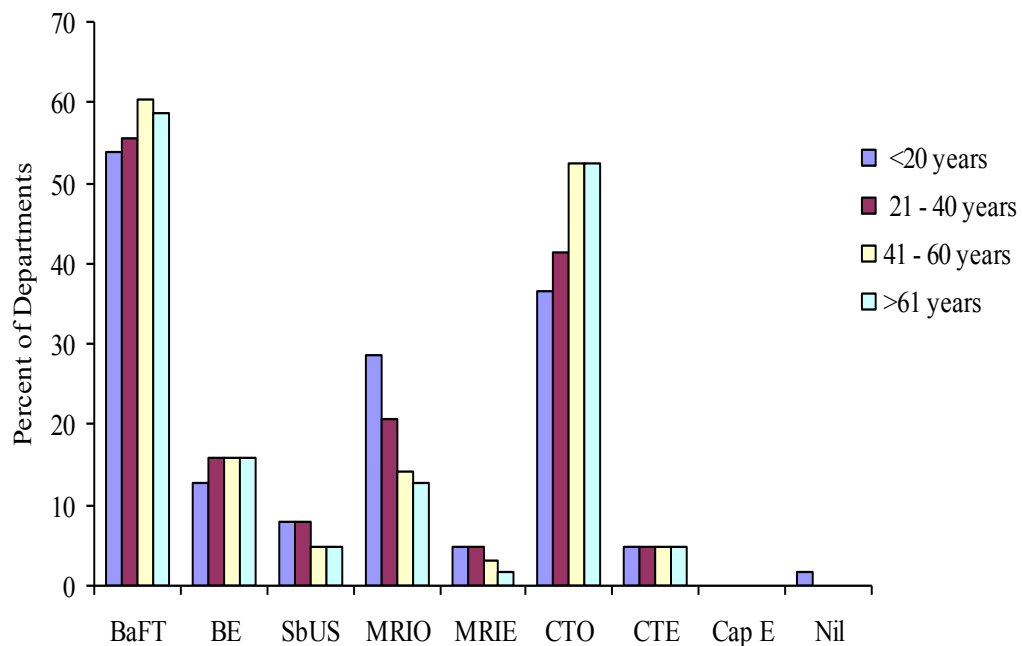


Figure 11: Investigations for patients with suspected small bowel obstruction. BaFT and CT are commonly performed, often concurrently and MR is performed with relative increased frequency in younger patients.

However, once again, when MRI was offered, it was mainly for younger patients instead of CT (18 [29%] of departments in those aged less than 20 years). Many departments suggested they would employ different tests concurrently (for example 20% would perform both BaFT and CTO).

Finally, for those with a clinically suspected flair in need of re-evaluation of the small bowel, whilst BaFT was the investigation of choice (35 [56%] of departments averaged across the age groups) CTO was used more frequently (21 [33%] of departments averaged across the age groups) compared to in those with newly diagnosed or suspected disease Small bowel ultrasound and MR were used more frequently in

patients of <20 years old, and then by 20 (32%) and 13 (21%) of departments respectively (Figure 12).

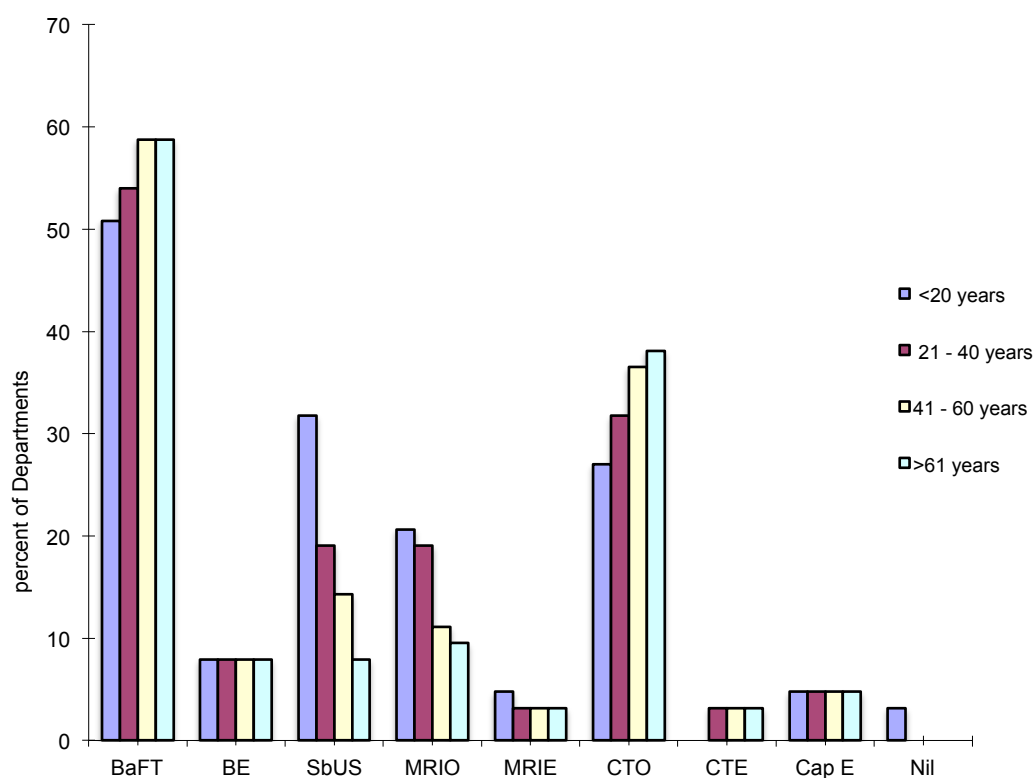


Figure 12: investigations performed in patients with clinical or biochemical disease flare up

2.1.3.3 Requesting of tests according to indications – Gastroenterologists

To assess disease extent in newly diagnosed Crohn's disease, BaFT was most requested modality (out of total 73 Gastroenterology departments 53 (73%) request it for patients > 41 and 45 (62%) for patients < 40). In 50% departments this was the only imaging requested. MRI was requested in 15 (21 %) departments for patients under 20 and SbUS was requested on average by 8 (11%) departments for patients < 40. Cap E was

requested by at most 6 (8%) of departments but almost always in combination with a radiological test. 70% of gastroenterologists requested a single investigation only in all age groups while up to 7 (10%) would not perform any investigation.

In patients with a high index of clinical suspicion for Crohn's disease, 59 (81%) of gastroenterologists would perform endoscopy and biopsy essentially regardless of age, of which around one third would also perform BaFT on the same patients. SbUS was the least frequently used imaging modality being requested by less than 10% of gastroenterologist across all age groups. MRI was most frequently requested in those less than 40 years and then by just 11 (15%) departments (Figure 13).

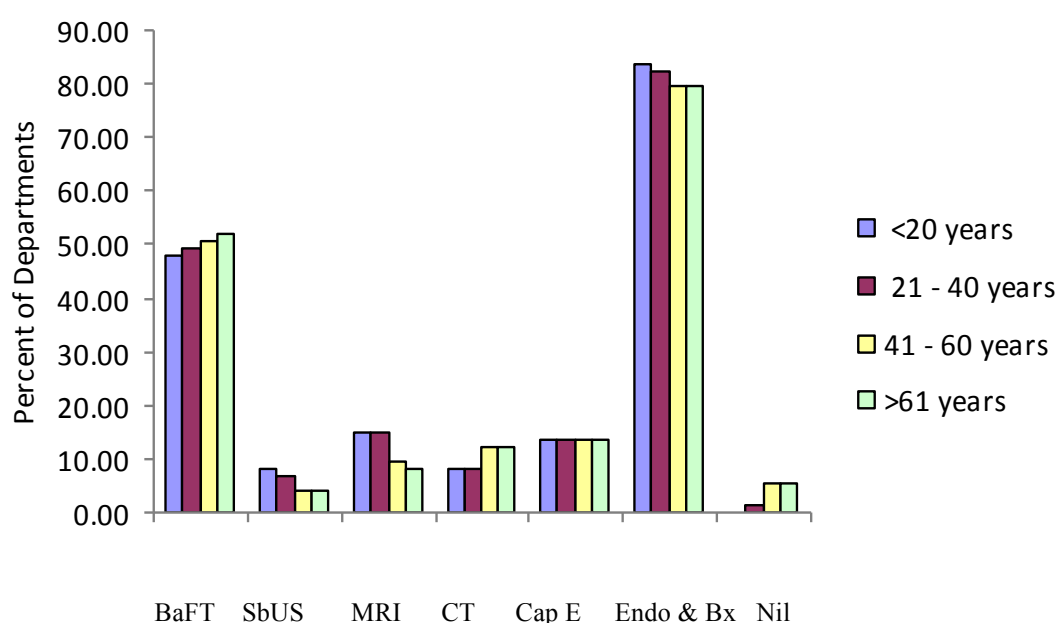


Figure 13: Investigations performed and/or requested by gastroenterologists in patients with high suspicion of CD. Endoscopy and biopsy with concurrent BaFT is preferred.

In patients with a low clinical index of suspicion, 14 (19%) departments would not perform any investigations. When investigations were request these tended to be similar

to those with high clinical suspicion, although SbUS was a little more frequently requested by 9 [12%] of departments in those aged below 40) (Figure 14).

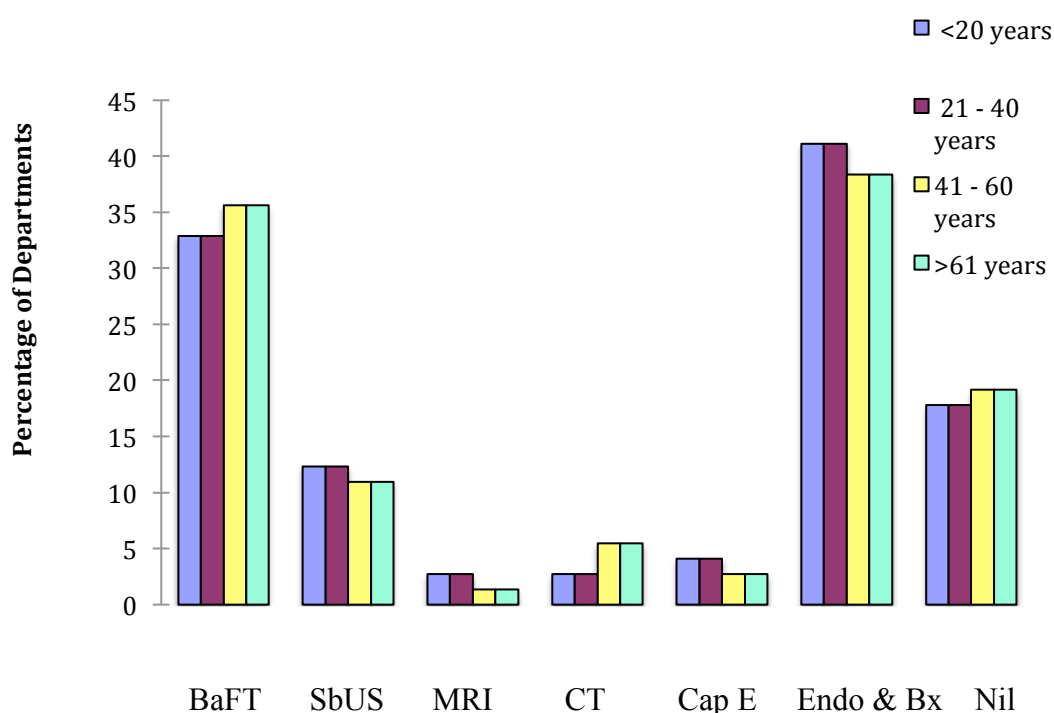


Figure 14: Investigations requested by Gastroenterologists in patients with low clinical suspicion of Crohn's disease

CT was requested by 41 (57%) of gastroenterologists when assessing suspected extraluminal disease regardless of age. BaFT was used by 29 (40 %) departments, while SbUS by at most 13 (17%) [In those aged less than 20]. However MRI was more popular, being requested by 22 (30%) in patients below the age of 20. Barium follow through was the investigation of choice for assessing obstruction requested by 50 (68) % of departments across all age groups (Figure 15).

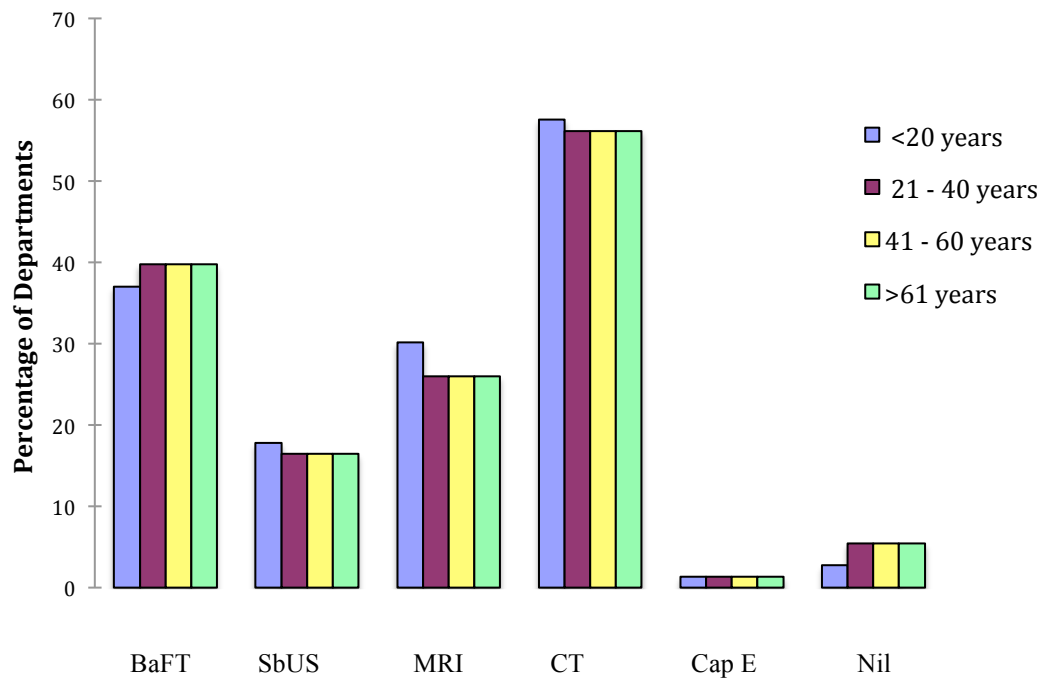


Figure 15: Investigations requested by Gastroenterologists in patients with suspected extra luminal complications in patients with Crohn's disease

When there was clinical evidence of a flare 17 (23 %) of gastroenterologists would not request further imaging. Across all age groups an average of 30 (41%), 4 (6%), 8 (10%) and 12 (16%) would however request BaFT, SbUS, MRI and CT respectively (Figure 16).

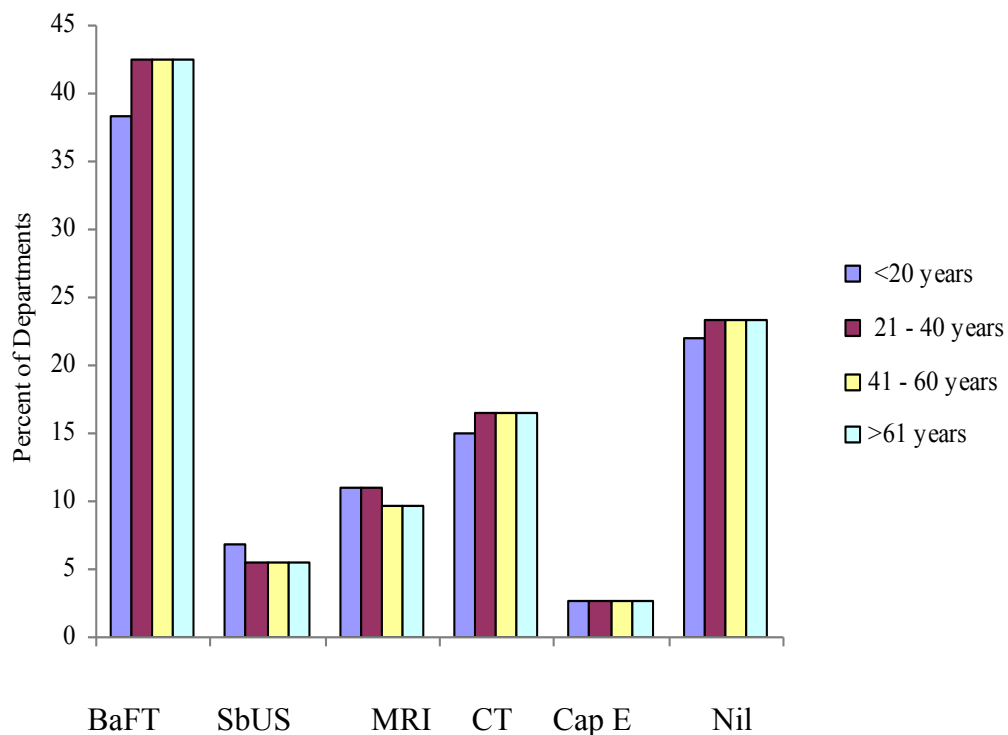


Figure 16: Investigations performed and/or requested by gastroenterologists in patients with suspected clinical flare. BaFT is the most frequently request examination

2.1.3.4 Comparison summary between radiologists and gastroenterologists

Barium follow remains the preferred small bowel imaging technique in all patient groups and use was similar between gastroenterologists and radiologists. There was also agreement in the use of CT as the primary modality in the assessment of extra luminal complications, although for assessment of obstruction radiologist were more likely to recommended CT than gastroenterologists request it.

However, radiologists were more likely to use SbUS and MRI when assessing patients both with suspected and proven disease, especially in patients <40 years (Figure 9 and 13).

2.1.4 DISCUSSION

For many years, barium follow through has been the routine radiological investigation for assessing known or suspected Crohn's disease of the small bowel. However, more recently there has been an increasing literature regarding the alternative use of cross sectional imaging techniques, notably SbUS, CT and MRI (section 1.2.3 and section 1.3.2.6). Potential advantages include the ability to better assess extramural complications, grade disease activity and in the case of ultrasound and MRI eliminate the radiation burden in this generally young patient cohort (162, 197, 198). Whilst European guidelines increasingly advocate the use of cross sectional techniques (particularly MRI and SbUS) anecdotal dissemination in the UK has been patchy and ad hoc.

Based on this survey data I have confirmed that barium studies remain the imaging investigation most commonly performed in both diagnosis and assessment of Crohn's disease in all ages. This is perhaps not surprising given their availability, relative simplicity and familiarity to both radiologists and gastroenterologists alike.

Furthermore, the examination remains very much part of the core curriculum training of UK radiologists, unlike more specialist investigations such as ultrasound and MRI, which as this survey shows are limited to less than 50% of UK departments. When performed well, it provides detailed analysis of the extent of diseased mucosal surfaces. It also has reasonable documented diagnostic performance, sensitivity and specificity of 85%-95% and 89%-94% respectively in the diagnosis of Crohn's disease (199). There is evidence that the level of interpretive performance for barium enema may be suboptimal in the UK (200). It is unclear whether small bowel fluoroscopy is suffering the same fate as the popularity of new cross sectional techniques increases. Although

the majority of UK Radiology departments now have access to MRI technology, in this survey only 38% offered MRI of the small bowel, mainly for those with known Crohn's or a high clinical suspicion. The aim of my survey was to assess current practice and as such, I did not complicate the questionnaire by collecting data on why one test was preferred over another. Although as discussed in third chapter of section none (1.3) recent Meta analysis data suggests MRI has high performance characteristics (190), it is important to state that although it is a theoretically attractive option in imaging Crohn's, there is no randomized trial data confirming its superiority over, or even equivalence to conventional barium investigations. Without this data it is likely that MRI small bowel provision will remain ad hoc, but certainly lack of interpretative expertise and scanner capacity likely contribute to the low level of dissemination. It is however interesting to note that radiologists were more likely to use MRI than gastroenterologists request it. Although knowledge of the technique and the supporting data is slowly increasing amongst UK radiologists, inevitably there will be a lag period as such information permeates through to the gastroenterological community. It is also interesting to note that although MR Enteroclysis likely has higher sensitivity than MR Enterography (190) the latter is significantly more widely utilized likely due to its greater simplicity and reduced invasiveness. Different oral contrast media has been used for the procedure such as bulk fiber laxatives mannitol, locust bean gum or a combination of both.

Forty-six percent of departments performed SbUS. Although ultrasound use for small bowel disease has been advocated for many years, it is clear the level of dissemination in the UK remains relatively low. The known reliance on expertise and associated steep learning curve (198) together with technical difficulties in obese or "gassy" abdomens have always limited uptake, as has the general reluctance of clinicians to request the examination (confirmed in this survey). However as noted in section 1.3.2.6, studies

investigating the diagnostic accuracy of US have shown reasonable results: sensitivity ranging between 84% and 90% and specificity between 98%-100 % (108, 113, 201-203). The rapidity and safety of ultrasound together with the relative accessibility of the terminal ileum in most patients likely explains the relatively frequent use by radiologists in excluding disease particularly in younger patients with a low underlying clinical suspicion. Its ability to assess disease activity and response to treatment by using colour flow Doppler and US contrast agents is also an advantage (204). Both MRI and SbUS tended to be offered more frequently in teaching hospitals.

CT was used infrequently in staging those either without a proven diagnosis of Crohn's or for assessing those with a new diagnosis. Similar to MRI, there is no hard data supporting the superiority of CT over other tests in this context, and of course the examination imparts a reasonable radiation burden in this generally younger patient cohort (194, 195). However, CT is currently preferred for detecting extraluminal complications (such as abscesses) by most radiologists and gastroenterologists despite the radiation dose. Extramural complications are well shown on CT, and it likely is the reference standard test for the detection of intra abdominal sepsis (205-208).

There was however evidence throughout the survey that radiation dose was a consideration by participants, as MRI and SbUS tend to be used more frequently in younger patient groups. However even in patients <20 years of age, tests using ionising radiation (especially barium follow through) were more frequently used for every indication listed.

It is of note that the use of capsule endoscopy was relatively infrequent even amongst gastroenterologists, confirming its role a very much a second line test in Crohn's disease.

The survey does have limitations. At best it can only be a snap shot of UK practice, and cannot detect changing trends in uptake of new imaging technologies-to do so will require a repeat survey in the future. The questionnaire return rate was relatively low but perhaps, not unexpected given the relatively detailed nature of the survey. I cannot however exclude the possibility that my sample is biased. Departments with an interest in small bowel imaging may for example have been more willing to reply. If anything, however such bias would perhaps tend to overestimate the use of new imaging technologies. In addition, this to my knowledge is the only such survey of UK small bowel imaging to date. Whilst I sampled radiology and gastroenterology departments separately, there was unavoidable overlap in the centers that responded but was only in 17 departments. Of course another limitation is that gastroenterologists were likely to have responded based on the knowledge which tests are available at their institution and which tests they “could get”. The survey may therefore underestimate their interest in new cross sectional imaging techniques such as MRI and USS and willingness to request them were they available. It would have been useful to ask gastroenterologists of their actual preferences for imaging and their knowledge of guidelines recommending the use of newer technologies. Finally as noted above, although responder was allowed free text space, I did not specially enquire as to reasons why one imaging test was preferred over another and what if any were perceived barriers to the introduction of new tests. However, it is relatively difficult to capture this data without introducing bias with the phraseology of questions, and my main aim was to produce a simple snap shot of the use of small bowel tests in the UK for various clinical indications.

In summary, based on my survey of UK radiology and gastroenterology departments, barium follow through remains the most frequently performed and requested examination for known or suspect luminal small bowel Crohn's disease, with CT being most frequently performed in those with suspected extra luminal complications. There has been only moderate dissemination of new small bowel technologies- MRI and small bowel USS are at present performed by a minority of UK imaging departments, particularly for patients aged less than 40 years. In general, radiologists are more likely to recommend MRI or USS than gastroenterologists are to request them. In the absence of hard trial data on which to base national guidelines, it is likely that uptake of MRI will remain rather patchy and ad hoc. The onus is on the radiological and gastroenterological communities to produce this evidence base to guide appropriate dissemination of new technologies such as small bowel MRI into standard clinic practice.

3 SECTION THREE: MRI IN IBD RELATED COLITIS

As discussed in chapter 1.3, magnetic resonance imaging (MRI) has shown considerable promise in quantifying inflammatory activity in Crohn's disease and ulcerative colitis involving small and large bowel (15, 212, 227). In section 2 the work covered the current use and impact of MRI in small bowel disease, a more established clinical indication. This section concentrates on use of MRI in the colon, for which clinical utility is less clear but impact could be as great as in the small bowel.

3.1 QUANTITATIVE MAGNETIC RESONANCE IMAGING OF COLONIC MURAL ENHANCEMENT: SEGMENTAL DIFFERENCES EXIST IN ENDOSCOPICALLY PROVEN NORMAL COLON

3.1.1 INTRODUCTION

When applied to the colon, most workers have used the technique of MR colonography (MRC) and as already described in section 1.3.3 various MRI parameters have been shown to correlate with disease activity, notably bowel wall thickness, T2 signal and contrast enhancement pattern. Absolute post gadolinium enhancement remains more controversial, with some workers finding high correlation (16), while others finding no

relationship (154). The reason for this variability likely includes differences in studied patient cohorts, applied standards of reference for disease activity (histological, biochemical, endoscopic or clinical) and methods of enhancement measurement (simple relative change in signal intensity at one time point or more complex quantitative dynamic contrast enhancement techniques). However, the baseline post contrast enhancement of normal (i.e. non inflamed colon) has received little attention. There are good reasons why enhancement may differ between bowel segments. Anatomical differences exist in segmental blood supply, the right colon is supplied via the superior mesenteric artery the left predominantly by the inferior mesenteric artery and the lower rectum via the iliac vessels (228). Colonic function also differs with proximal colon providing much of the water absorptive capability of the colon (229).

In 15 normal volunteers, Ajaj et al have shown that at a single time point post contrast (75 seconds), relative enhancement differs according to colonic segment (being highest in the rectum and sigmoid and lowest in the right colon and descending) (15).

Clearly inter- segmental differences of normal colon enhancement will influence the interpretation of MRI in inflammatory bowel disease, in particular when assessing potentially inflamed bowel. The purpose of this study was to present and discuss the quantitative MRI changes that occur following enhancement of endoscopically proven normal colon and to assess inter- segmental differences.

3.1.2 MATERIALS AND METHODS

8 patients (4 females, mean age 45, range 25 to 57) with no known history of inflammatory bowel disease and undergoing conventional colonoscopy were recruited to undergo additional MRC on the day of their conventional examination.

3.1.2.1 Patient preparation

All patients underwent solid food restriction from lunchtime the day before colonoscopy followed by full bowel purgation- 10 Senna tablets and two sachets of magnesium citrate (Citramag- Sanochemia Diagnostics, UK) dissolved in one litre of water. MRC was performed by the thesis research fellow (Rehana Hafeez) 2 hours before colonoscopy in all patients. Following rectal introduction of 16F Foley catheter, the colon was gently filled with 1.5l of warm tap water from an enema bag held at shoulder height (i.e. filling by gravity). Bowel motility was abolished by intravenous spasmolytic (Buscopan, Boehringer Ingelheim, Germany) 0.3mg/kg (maximum 20 mg) immediately prior to abdominal imaging.

3.1.2.2 MRI protocol

Images were acquired in the prone position with a 1.5T Siemens Avanto (Avanto; Siemens, Erlangen, Germany) magnet using the body and spine array coils.

The pre – contrast T1 relaxation time of colon was measured by using three breath-hold coronal fat saturated 3D Fast Low Angle Shot (FLASH) images of the abdomen and pelvis with different excitation flip angles (flip angles 5°, 10°, and 35°) (table 24) (230)

Prior to intravenous contrast administration, three 3D FLASH baseline sets of coronal images were acquired during suspended inspiration (table 21). A single dose of (0.2 mg/Kg) IV gadoterate meglumine (Dotarem; Guerbet Roissy, France) was then injected into an arm vein at 3 mL/sec, followed by a saline chaser (10 mL). At injection the patient was asked to hold his/her breath for 20 seconds (during which a single 3D FLASH volume dataset was acquired), followed by 10 seconds of gentle breathing, immediately followed by another 20 seconds breath hold acquisition and 10 seconds of gentle breathing. The acquisition protocol was repeated to generate a total of 8 post

contrast 3D FLASH datasets.

	*FLASH 3D (T1 calculation)	*FLASH 3D (Pre-contrast)	*FLASH 3D (Post-contrast)
TE (ms)	2.4	2.4	2.4
TR (ms)	5.15	5.15	5.15
FA (degrees)	5°, 10°, 35°	35°	35°
NEX	1	1	1
iPAT	2	2	2
FOV (mm)	500x500	500x500	500x500
STH	3	3	3
No. slices	48-60	48-60	48-60
BW (Hz)	300	300	300
Acq. Matrix	256x154	256x154	256x154
Recon. Matrix	512x512	512x512	512x512
TA (s)	17	17	17
No. Acq.	**1	3	8

Table 21: MR Acquisition Parameters

*Breath held fat saturated coronal T1 weighed 3D Fast Low Angle Shot

**Single acquisition at each flip angle

TR- repetition time, TE- echo time, FA- flip angle, NEX- number of signal

Averages, iPAT- parallel imaging factor, FOV- field of view,

STH- slice thickness

BW- pixel bandwidth, TA- Time for single 3D FLASH acquisition.

3.1.2.3 Colonoscopy

Indications for colonoscopy for recruited patients were change in bowel habits (n=3), previous history of colonic polyps (n=3) and PR bleeding (n=2).

Patients remained nit by mouth following MRC for a further 1 to 2 hours while awaiting colonoscopy performed by experienced (2-10 years) operators. Intravenous sedatives (Midazolam 50 microgram/kg, max 10 mg and Fentanyl 100 mcg) were administered, together with nasal oxygen. All patients had multiple ileo- colonic biopsies taken to exclude microscopic colitis. None of the patients had any complication and all were discharged within few hours. None of the biopsies showed features of inflammation.

3.1.2.4 MRI data analysis

Region of Interest (ROI) analysis was performed on 3D FLASH MR Images using the open source OsiriX medical imaging platform (<http://www.osirix-viewer.com>). Single freehand linear ROIs (mean size, 5.4 cm; range 2.3 to 9.8cm) were located in the colonic wall of the ascending colon, descending colon and lower rectum by a radiologist (Shonit Punwani) and thesis author in consensus (Figure 24). These segments were chosen as representative of the known differing vascular supply and functional properties of the colon over its length. To guide ROI placement, the observers first reviewed the whole MR contrast dataset and chose those parts of the bowel wall reliably identifiable throughout the time series. In order to maintain the ROI within the colonic wall between successive acquisitions, the shape of the linear ROI was altered (with the length [± 0.01 cm] and anatomical position kept constant) to account for any colonic deformations.

The mean ROI signal intensity was recorded for each segment. The signal from the three pre-contrast baseline acquisitions for a given ROI was averaged, provided a single

pre –contrast ROI signal intensity for colonic each segment. T1 was calculated for each segment in Microsoft Excel for Mac (2011) using the expression for the evolution of signal intensity in spoiled gradient echo and solving for T1 (230). The T1 relaxation rate (R1) was derived by $1/T1$.

3.1.2.1 Statistical Analysis

The mean R1 (n=8 patients) prior to contrast and at each of the 8 post-contrast time points was used to generate an enhancement (R1-time) curve for the three colonic segments.

The initial change in R1 ($\Delta R1$) was calculated between the 10 (1st post-contrast) and 40 seconds (2nd post-contrast) time points.

Early ‘plateau phase’ post-contrast R1 was derived as the average of the 40, 70 and 100s measurements for each segment. Late ‘plateau phase’ post-contrast R1 was calculated as the average of the 130,160,190 and 210 measurements.

The area under the R1- time curve (AUC-R1) was determined using Prism (GraphPad Prism version 4.00 for Mac, GraphPad Software, San Diego California USA, www.graphpad.com)

The Shapiro- Wilks test was applied to the data and a normal distribution confirmed. A student’s paired t-test was therefore used to compare R1 at pre-contrast, $\Delta R1$, early and late post-contrast plateau phase R1, and the AUC-R1 between the individual colonic segments.

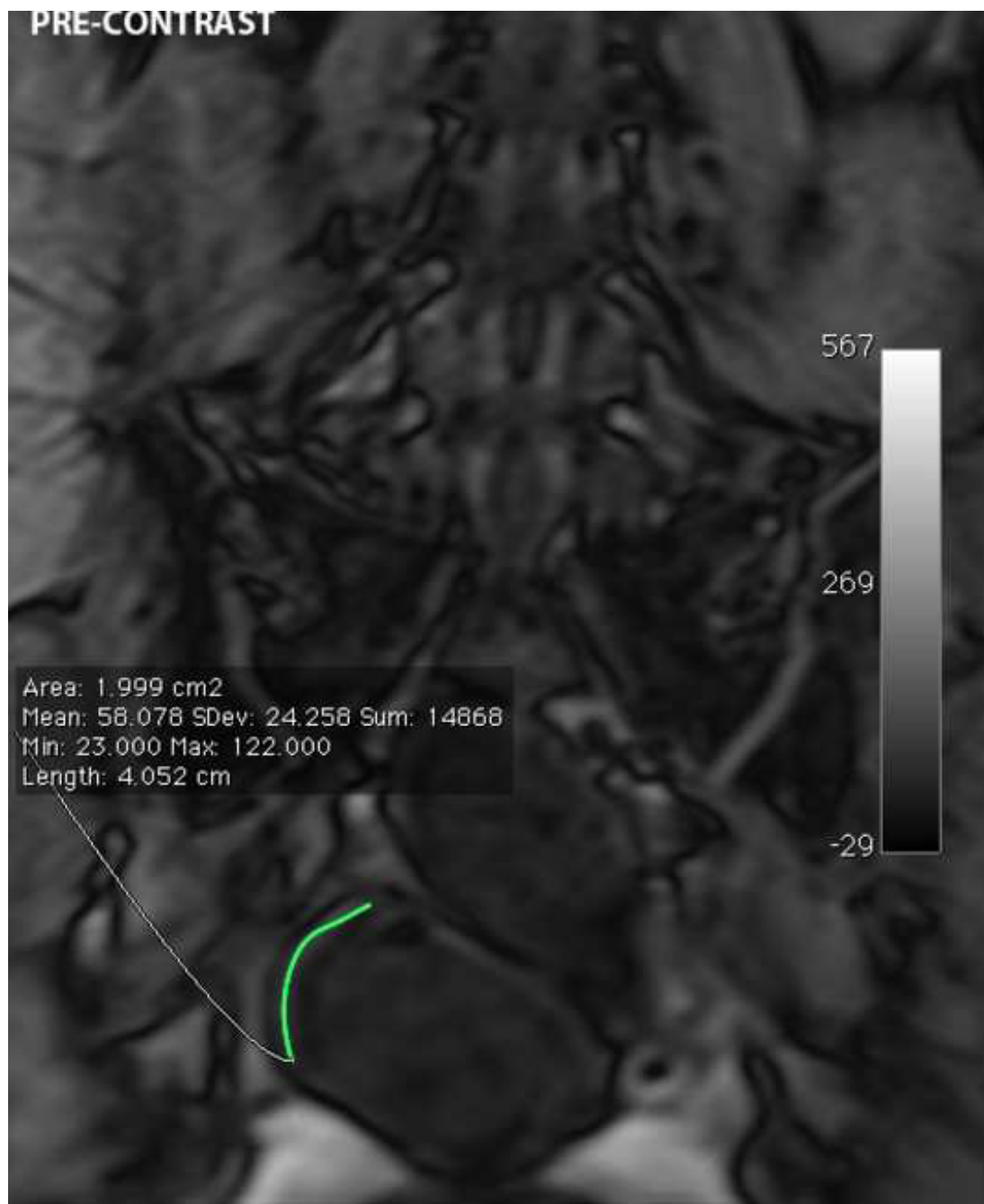


Figure 17 (a): Region of interest placement was performed using OsiriX. Pre-contrast coronal T1 weighted VIBE image of a rectum with a linear region of interest placed within the rectal wall.

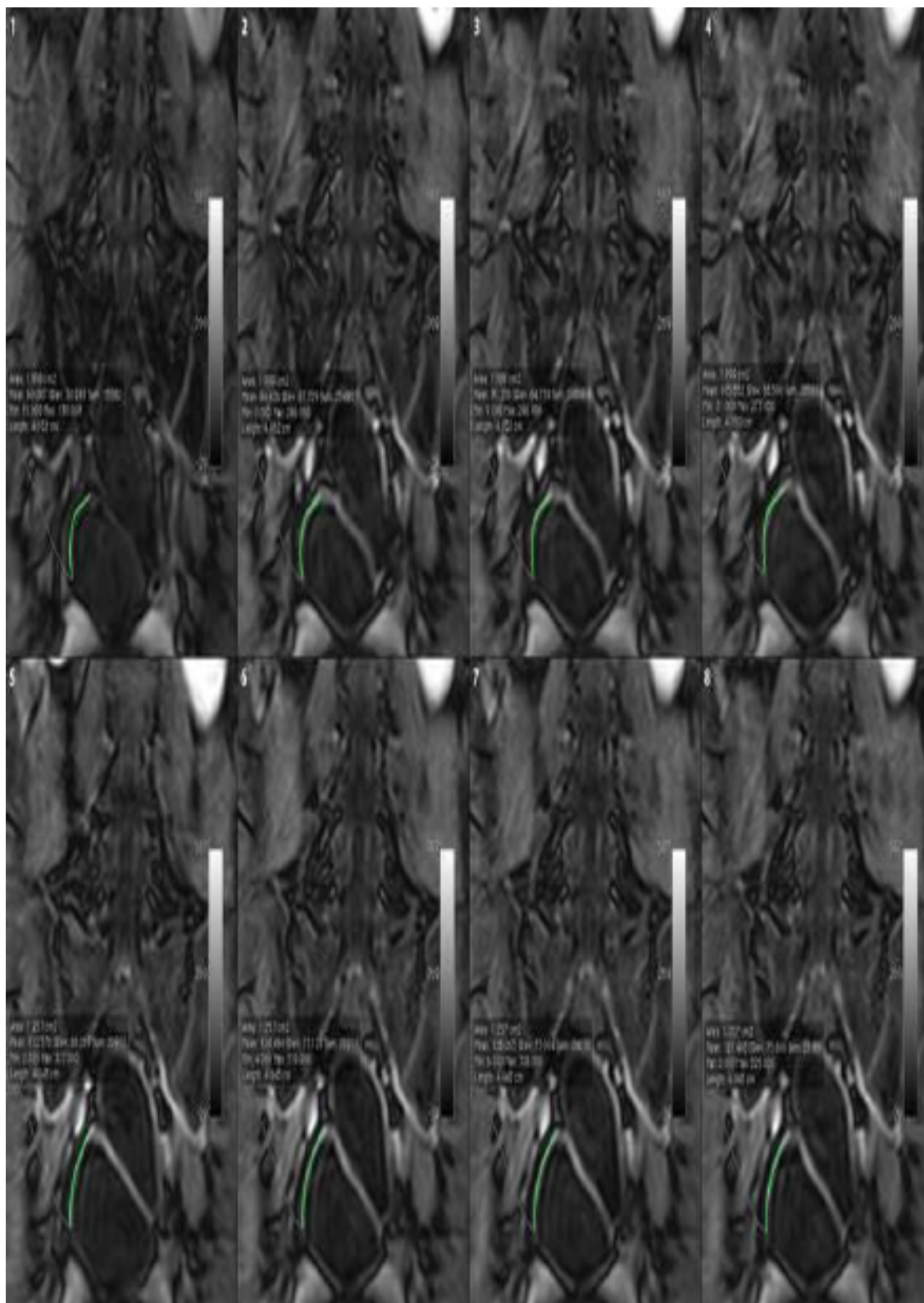


Figure 17(b): Matched post-contrast 10, 40, 70, 100, 130, 160, 190, 220 second (1 to 8 respectively) images demonstrating the linear region of interest on successive acquisitions.

3.1.3 RESULTS

All colonoscopies were complete to the terminal ileum and normal, with no evidence of inflammatory bowel disease on direct inspection or biopsy.

The mean pre-contrast T1 of ascending colon, descending colon and rectum were 606 ± 264 , 661 ± 264 and 680 ± 300 ms respectively.

R1-time curve for ascending colon, descending colon and rectum are illustrated in figure 25. Pre-contrast there was no significant difference of R1 values between individual segments (table 22). $\Delta R1$ was greater for the ascending than descending colon (table 17, $p=0.03$). There was no significant difference in $\Delta R1$ for other colonic segments (table 22).

Early and late post-contrast plateau phase R1 values were not significantly different between bowel segments (table 22).

The AUC-R1 of the ascending colon was significantly greater than the descending colon (table 16, $p=0.03$). There was significant difference of AUC-R1 between the rectum and other colonic segments (table 22).

	Ascending Colon	Descending Colon	Rectum
Pre – contrast T1 (ms⁻¹)	606±244	661±264	680±300
Pre-contrast R1(ms⁻¹)	0.0019±0.0007	0.0023±0.0021	0.0018±0.0004
ΔR1 (ms⁻¹)	0.0042±0.0010	0.0033±0.0015	0.0048±0.0025
Early post-contrast R1 (ms⁻¹)	0.0042±0.0010	0.0033±0.0015	0.0048±0.0025
Late post-contrast R1 (ms⁻¹)	0.0049±0.0021	0.0036±0.0015	0.0049±0.0024
AUC-R1	0.54±0.19	0.30±0.14	0.60±0.46

Table 22 (a): Quantitative MR colonic segmental parameters

	Ascending vs. Descending t-test (p-value)	Ascending vs. Rectum t-test (p-value)	Descending vs. Rectum t-test (p-value)
Pre-contrast R1 (ms⁻¹)	0.50	0.62	0.49
ΔR1 (ms⁻¹)	0.03*	0.48	0.07
Early post-contrast R1 (ms⁻¹)	0.21	0.60	0.24
Late post-contrast R1 (ms⁻¹)	0.08	1.0	0.30
AUC-R1	0.03*	0.14	0.75

Table 22(b): Comparison of colonic segments

*Significant difference at the p<0.05 level.

ΔR1 is the change in R1 between the 10 (1st post-contrast) and 40 seconds (2nd post-contrast) Acquisitions.

AUC-R1 is the area under the R1-time curve.

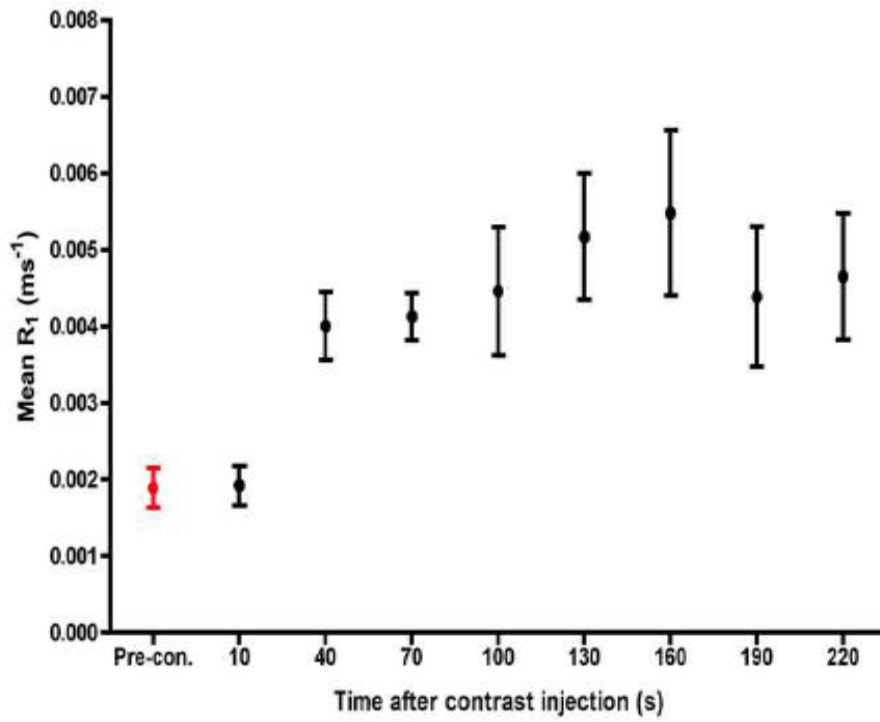


Figure 18 a: R1- time curve for ascending colon

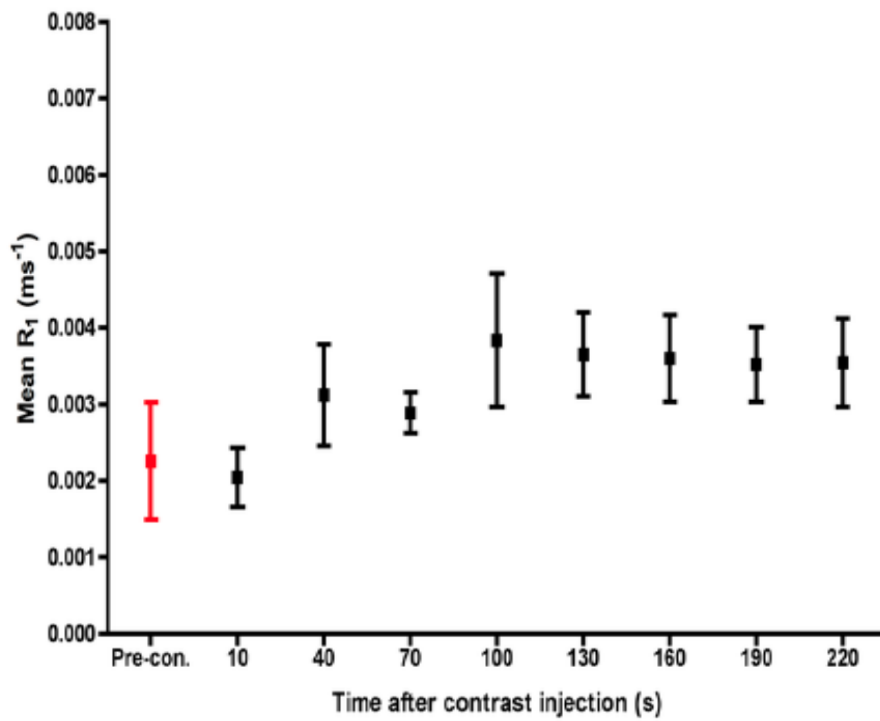


Figure 18 b: R1-time curve for Descending colon

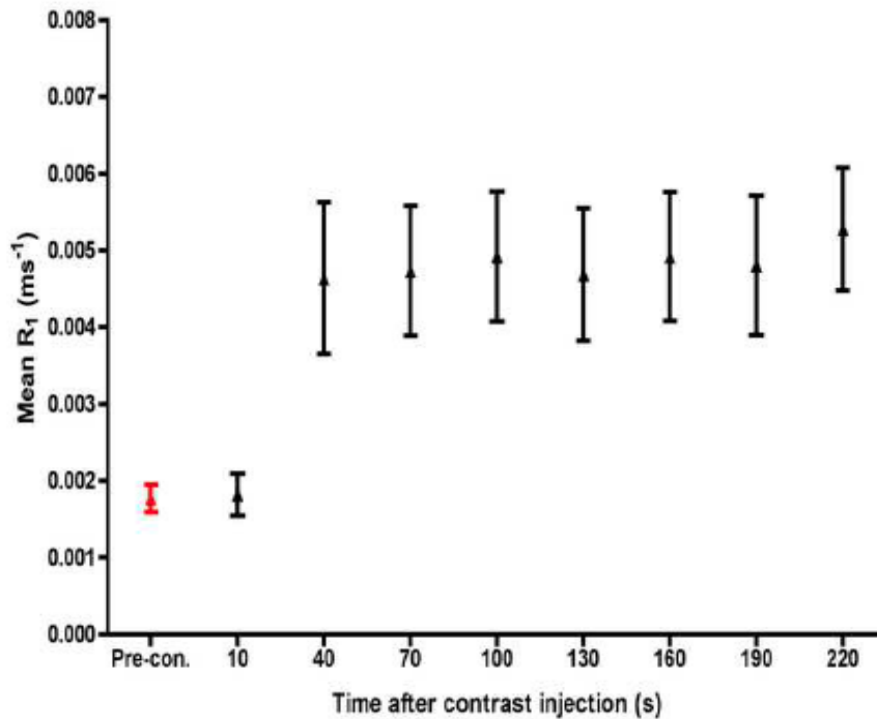


Figure 18 c: R1-time curve for Rectum

3.1.4 DISCUSSION

T1 relaxation is a consequence of fluctuations in the magnetic field experienced by individual hydrogen nuclei, which in the body are predominantly bound within water molecules. As each hydrogen nucleus has magnetic properties, the rotational and tumbling movements of water molecules themselves act as the main source of magnetic field fluctuations. For effective T1 relaxation, the oscillations in magnetic field have to occur at a specific frequency called the Larmor frequency. The greater the number of hydrogen nuclei experiencing fluctuations at the Larmor frequency the shorter the T relaxation time and the brighter the signal. The number of oscillations at the Larmor frequency is greater for water contained within soft tissues as compare to pure water or solid structure. The study found that mean pre-contrast T1 of normal colonic segments

was 606 to 680 ms with a narrow range and that there was no significant inter-segmental difference between R1 ($1/R1$), reflecting the nature of the T1 relaxation mechanism.

Gadolinium based contrast agents work by producing additional magnetic field oscillations at the Larmor frequency thereby further shortening the T1 relaxation time and increasing signal within the image. For the effects of contrast agents to be realized, they must be in close proximity of water molecules. When confined within the vasculature, the number of water molecules affected is limited. With free leakage into the interstitium, more tissue water is exposed to the T1 shortening effects.

The study found significant difference between colonic segments in their behavior following gadolinium administration. Notably $\Delta R1$ and AUC-R1 were greater for the ascending than descending colon. By way of explanation, Skinner et al using vascular casts of normal colon showed a higher micro vascular volume ($13.4 \pm 3\%$ and $7.7 \pm 2.2\%$ respectively) and micro vascular surface area ($22.4 \pm 5\%$ and $17.5 \pm 6.9\%$ respectively) in the proximal colon compared with the distal colon (231). A higher percentage vascular volume in the proximal colon would mean that there is proportionally more intravascular water upon which intravascular gadolinium can act. Furthermore, considering dynamic contrast enhanced models the volume transfer coefficient (K_{trans}) is the product of capillary permeability and surface area where blood flow is not limited (232). As the micro vascular surface area of the proximal colon is greater than distal colon (231) it follows that K_{trans} should be higher (assuming the vascular permeability is equal or higher). A larger K_{trans} signifies, that intravenous contrast will pass more freely

into the interstitial space exposing more tissue water to the gadolinium induced T1 relaxation effects likely accounting for the greater increase in R1 (larger $\Delta R1$) of ascending colon compared with descending colon.

Ajaj et al found that prior to IV contrast there was no difference between the contrast to noise ratio of different colonic segments, and at 75 seconds following IV contrast enhancement was highest in the rectum and sigmoid, and lowest in the ascending and descending colon (15). This study partially supports their findings, as no difference was found in R1 between segments prior to contrast and a relative lower enhancement within the descending colon. However discrepant to Ajaj et al, no significant difference was found between rectum and ascending colonic R1 changes, and R1 change within the ascending colon was higher than descending colon. By way of explanation, it is possible results were influenced by the differences in acquisition and analysis of the MR data between the two studies. In contrast to Ajaj et al, enhancement differences evaluation was done between segments based on quantitative R1 change in order to avoid the effect of spatial signal intensity variation that can occur across images; and the potential difficulties with noise assessment within images where parallel imaging or image filters have been used (233).

The purpose of the study was to assess whether segmental variations are present in the enhancement of normal colon. Whilst these results present quantitative measurements performed on a total of eight normal patients at a single center (UCLH), they nevertheless illustrate statistically significant difference between colonic segments that support the anatomical and functional differences within the colon. Furthermore, a

robust selection standard was used, ensuring all these patients had confirmed normal (non-inflamed) colonic appearances at endoscopy. The study also intentionally limited analysis to segments with clearly defined regional blood supplies and functional specializations. I acknowledge that further recruitment is necessary to investigate the segmental differences that are “near statistical significance” in these results. Indeed the small sample size and large standard deviation between measurements means we must treat the data with some caution-it is possible difference in significance between ascending and descending colon be a reflection of the differences in standard deviation of the baseline data. However there was no significant difference between pre-contrast segmental RI values, despite the relatively large standard deviations of the data. Such changes only became apparent following contrast administration.

In conclusion my results highlight that inter-segmental differences in colonic enhancement are present. These should be considered when using enhancement as a biomarker for colonic inflammation as not all differential segmental enhancement is a result of inflammation.

3.2 ASSESSMENT OF COLONIC DISEASE ACTIVITY IN INFLAMMATORY BOWEL DISEASE USING MRI COLONOGRAPHY

3.2.1 INTRODUCTION

Rational use of immunosuppressive therapies in IBD disease relies on accurate identification of those patients with acute inflammation –so called “active disease” who are most likely to respond to the treatment, together with assessment of the disease extent. The management of colonic IBD and assessment of response to medication largely depends on accurately documenting the location, extent, and the severity of the inflammation.

As discussed in section 1.2.3, unfortunately there is no reliable, non-invasive method to identify such patients. Clinical assessments based on patient symptomatology (e.g. CDAI), biomarkers and endoscopy. As already described in section 1.3.3, MR Colonography has been advocated as a potentially useful investigation for this purpose. Several qualitative MRI scoring systems for assessing inflammatory activity in IBD are beginning to appear in literature.

For example Steward et al have described a simple and rapid qualitative scoring system which has been developed and validated in patients with small bowel CD by using a robust transmural histological reference standard of inflammation (234). In this study data from 16 patients was used to derive the MRI score. All these patients had gone elective surgery for CD and had pre operative MRE. An MRI was performed of the resected specimen and used to accurately co- locate sites of full transmural histological sampling with regions of interest placed within the bowel on the pre –operative MRI.

The pathological reference standard of inflammation was based on ulceration and the extent and depth of neutrophilic infiltration and a transmural histopathological acute inflammation score (AIS) was assigned.

Qualitative measurement were taken on pre operative MR images according to a qualitative scoring system which included mural thickness, mural T2 signal intensity, perimural oedema (Fat saturated half- Fourier RARE images), bowel wall enhancement (VIBE images 70 seconds post contrast) using adjacent normal bowel wall as reference. Using a regression analysis with backward selection, the authors proposed the final index which best predicted histological AIS was

$$= 1.79 + 1.34 \text{ Mural Thickness (in mm)} + 0.94 \text{ mural T2 score}$$

(R squared = 0.52)

This score was then validated in a sample of 26 patients who had MRE and endoscopy with terminal ileum biopsy within four weeks. The MRI score was calculated for terminal ileum of each patient. In all patients endoscopic biopsy was taken from the terminal ileum and acute inflammatory score assigned (eAIS) (again mainly based on ulceration and extent of neutrophilic infiltration see table 28 below). There was a significant correlation between MRI index and histopathological eAIS (Kendall's tau b = 0.4, 95% CI = 0.11 to 0.64, p=0.02).

This score has recently been modified by the authors to take into account the length of affected bowel in each segment (as apposed to a single point estimate) as well as extra enteric complications (235). This “MRI activity score” is further detailed in the methods of this chapter below.

An alternative system has been proposed by Rimola et al (16, 187) and already described in section 1.3.4. Rimola used the CDEIS as reference for disease severity to

derive and validate their qualitative MRI score (MaRIA) based on wall thickness, relative contrast enhancement (RCE) and presence of oedema.

$$\text{MaRIAS} = 1.5 \text{ wall thickness} + 0.02 \text{ RCE} + 5 \text{ oedema} + 10 \text{ ulceration}$$

This index showed correlated with CDEIS ($r=0.82$, $p<0.001$) and in second study they validated the same score in a new patient cohort [MaRIA correlated with CDEIS ($r=0.798$, $p<0.001$ per segment and $r=0.87$, $p<0.001$ per patient) Harvey – Bradshaw index ($r=0.56$, $p<0.001$) and CRP ($r=0.53$, $p<0.001$)].

The utility of these scoring systems is yet to be fully tested. For example the scoring system described by Steward was based on small bowel disease and its applicability to the colon is unknown. Although Rimola et al have validated their score in a new patient cohort, these were recruited from the same center and the data was analyzed by the same clinical and radiological teams. A true test of any scoring system is if it can be reproduced in a completely new patient population by a different clinical group.

Therefore, the purpose of this study was to apply these proposed MRI scores of small bowel Crohn's disease activity in a new patient cohort recruited at UCLH and evaluate their ability to predict colonic disease activity against a reference standard of Endoscopy (CDEIS), Histology grading and eAIS.

3.2.2 MATERIALS AND METHODS

Twenty one patients with colonic inflammatory bowel disease undergoing endoscopy as part of normal clinical care were recruited to undergo prior MRC. One patient was incontinent of the water enema and excluded. Among 20 patients 10 females (mean age 35 range 16-50) and 10 male patients (mean age 42 range 29-63) took part in the study.

	New suspected cases	Follow up
Total	5	15
Males	02	07
Females	03	08
UC	02	08
CD	03	07

Table 23: Patients for MRC

3.2.2.1 Eligibility criteria

Patients undergoing endoscopy for IBD related indications, notably

- a) Known previous histopathological diagnosis of CD or UC undergoing investigation for restaging of disease, disease extent or assessment of response to therapy
- b) High clinical suspicion of IBD based on clinical examination and current investigations (biochemical or radiology [CT, MRI, Barium studies, ultrasound])
- e) Age 16 or over

3.2.2.2 Exclusion criteria

- a) Pregnancy
- b) Contraindication to MRI (pacemaker, metallic implant, severe claustrophobia etc.)
- c) Patients with history of renal impairment (theoretical risk of nephrogenic systemic fibrosis with gadolinium), active ischemic heart disease and acute glaucoma.

3.2.2.3 MRI protocol

Patients had undergone bowel preparation deemed necessary for their conventional endoscopy, and this was not altered. All the patients underwent MRColonography 2 hours before colonoscopy according to standard MRC protocol (Appendix C).

3.2.2.4 Endoscopy and reference

Endoscopy was performed as per usual practice, in the endoscopy unit by the experience operators (2-10 years experience). All the patients remained nil by mouth for 1-2 hours after MRC while waiting for CC. Intravenous sedatives (Midazolam 50 microgram/kg, max 10 mg and Fentanyl 100 mcg) was administered, together with nasal oxygen. The operators completed a validated Crohn's Disease Endoscopic Index of Severity (CDEIS) study proforma, documenting the endoscopic severity of the colonic disease. The endoscopic scoring system utilized is based on variables such as ulceration, area of surface involved by disease and ulceration and presence of stenosis (ulcerated or non ulcerated) (see section 1.2.3.3.1 for full definition of the CDEIS). Three patients had flexible sigmoidoscopy as a planned procedure and 17 had complete CC.

3.2.2.5 Histopathology and reference

The biopsies taken during the endoscopy were sent for histological assessment. An experienced histopathologist (M Justo Rodriguez) scored the biopsies for inflammation using standard five grade classification system for inflammation (defining the degree of inflammation according to the presence of inflammatory cells in lamina propria and epithelium and crypt destruction, ulceration and abscess formation) (236) (Table 24).

Grade	Definition	Features
Grade 1	Minimal active	Increase in inflammatory cells in the lamina propria (lymphoplasmacytic).
Grade 2	Mildly active	Presence of neutrophils/eosinophil but confined to the lamina propria
Grade 3	Moderately active	Neutrophils within epithelium (crypt or surface) but no crypt abscess formation
Grade 4	Markedly active	As in 3 but with crypt destruction and abscesses
Grade 5	Severely active	As in 4 with erosions/ulcerations

Table 24: Histopathological Inflammatory grading system

In addition an alternate grading system of histopathological inflammation (eAIS) previously devised by the pathologist and used in the work by Steward et al was assigned to each biopsy (234) (Table 25).

Histological variable	Grade
Erosion or ulceration	0= No, 1= yes
Polymorphs in lamina propria	0= No, 1= yes
Cryptitis	0= No, 1= yes
Crypt abscess formation	0= No, 1= yes
Inflammatory exudates	0= No, 1= yes
Granulomas	0= No, 1= yes

Table 25: eAIS

3.2.2.6 Data analysis

Data analysis was performed on Images using the open source OsiriX medical imaging platform (<http://www.osirix-viewer.com>) as in section 3.1.2.3, in consensus by a GI Radiology research fellow (Jessica Makanyanga) and the thesis author (Rehana Hafeez). Example images of the various scoring categories were made available to the observers from the original publications of Steward (234) and Rimola (16, 187) to help standardize the grading of the datasets. A consultant radiologist Prof Stuart Taylor (10 years of abdominal MRI experience) closely supervised the scoring process by the observers, although a formal inter-reader agreement analysis was not performed.

In all 20 patients the colon was divided into six segments (caecum, Ascending colon, transverse colon, descending colon, sigmoid and rectum) using standard anatomical definitions for the purpose of data analysis.

3.2.2.6.1 Steward Score

The two observers scored qualitative observations in all six segments according to the previously derived and validated scoring system for CD described by Steward et al and based on wall thickness and T2 signal (Table 29) (Figure 19 a & b).

MRI index was calculated for each segment as:

$$1.79 + 1.34 \text{mural thickness} + 0.94 \text{ mural T2 score}$$

The individual segmental scores were added to get the final score for each patient.

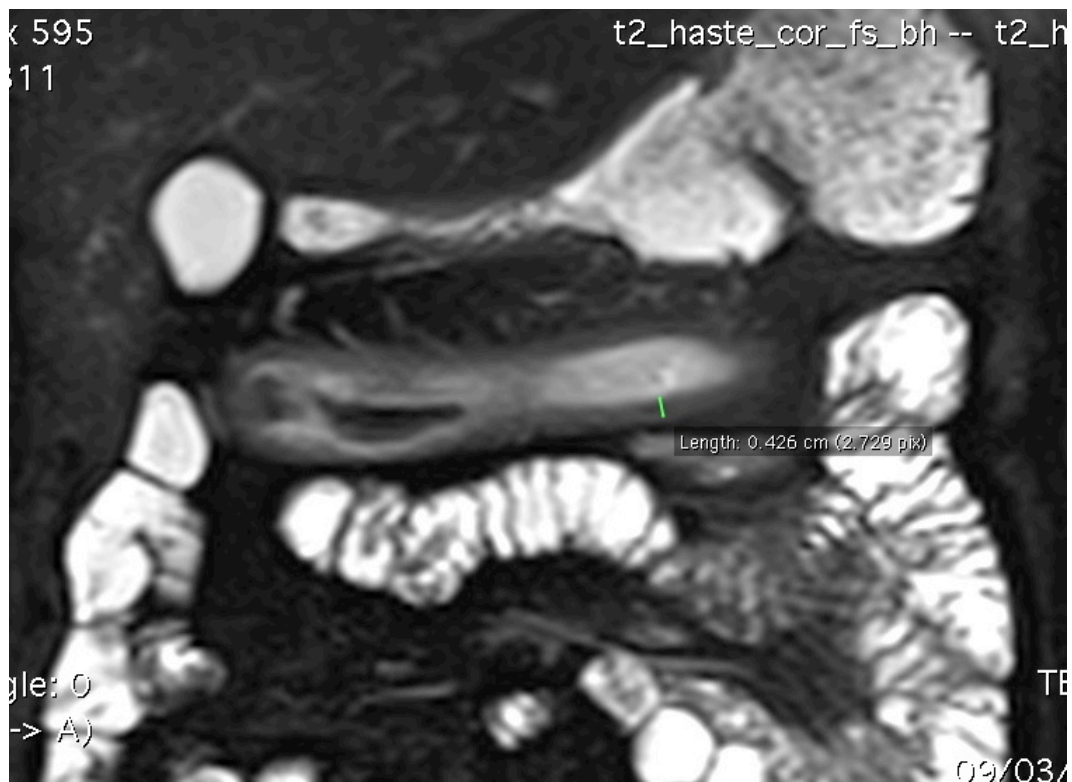


Figure 19 a: Mural thickness – Transverse colon

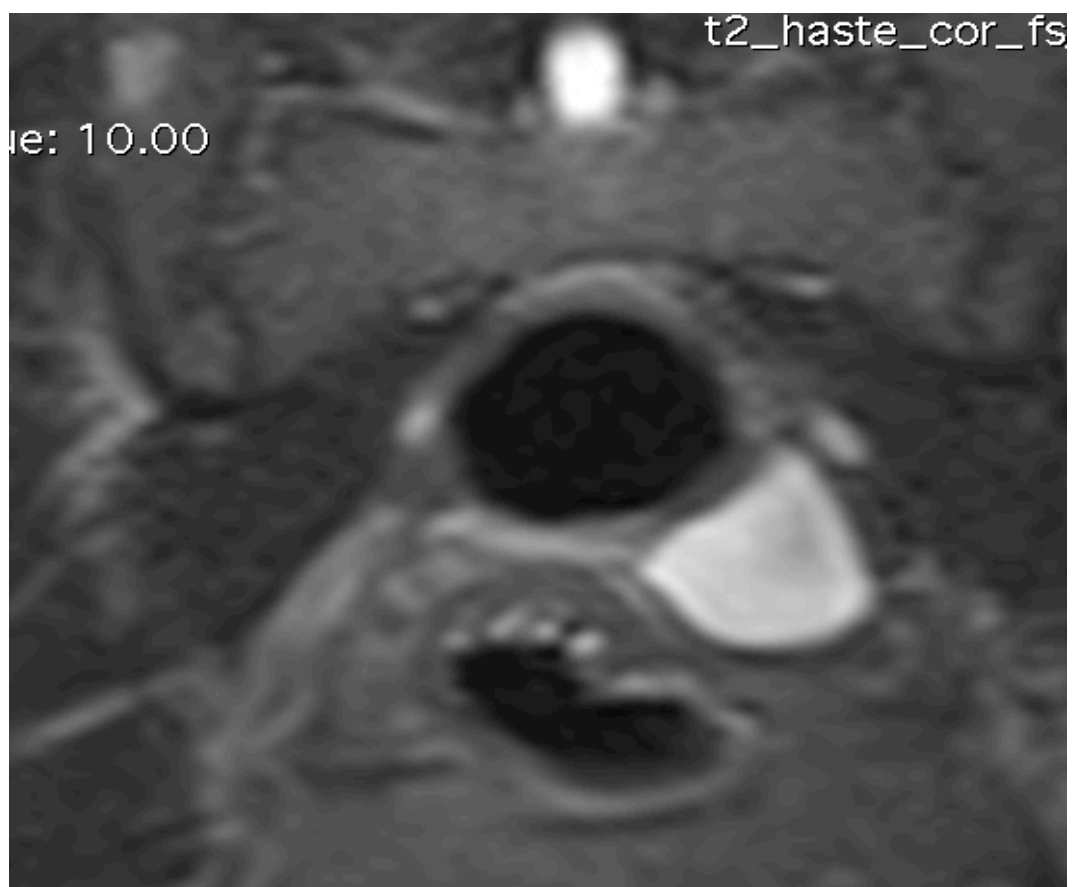


Figure 19 b: Increase mural T2 signals

Score	0	1	2	3
Mural thickness	1-3 mm	>3-5 mm	>5-7 mm	>7mm
Mural T2 signal	Equivalent to normal bowel wall	Minor increase in signal – bowel wall appears dark grey on fat saturated images	Moderate increase in signal- bowel wall appears light grey on fat saturated images	Marked increase in signal- bowel wall contains areas of white high signal approaching that of luminal contents

Table 26: Qualitative parameters used to calculate Steward score

3.2.2.6.2 MRI activity score

The MRI activity score was assigned to each of the 6 colonic segments by the observers in consensus according to following definitions (Table 27) (Figure 20).



Figure 20 a: T1 weighted imaging – Dark lumen MRC



Figure 20 b: Mural thickness score 2



Figure 20c: Mesenteric edema score 2 (small pool)

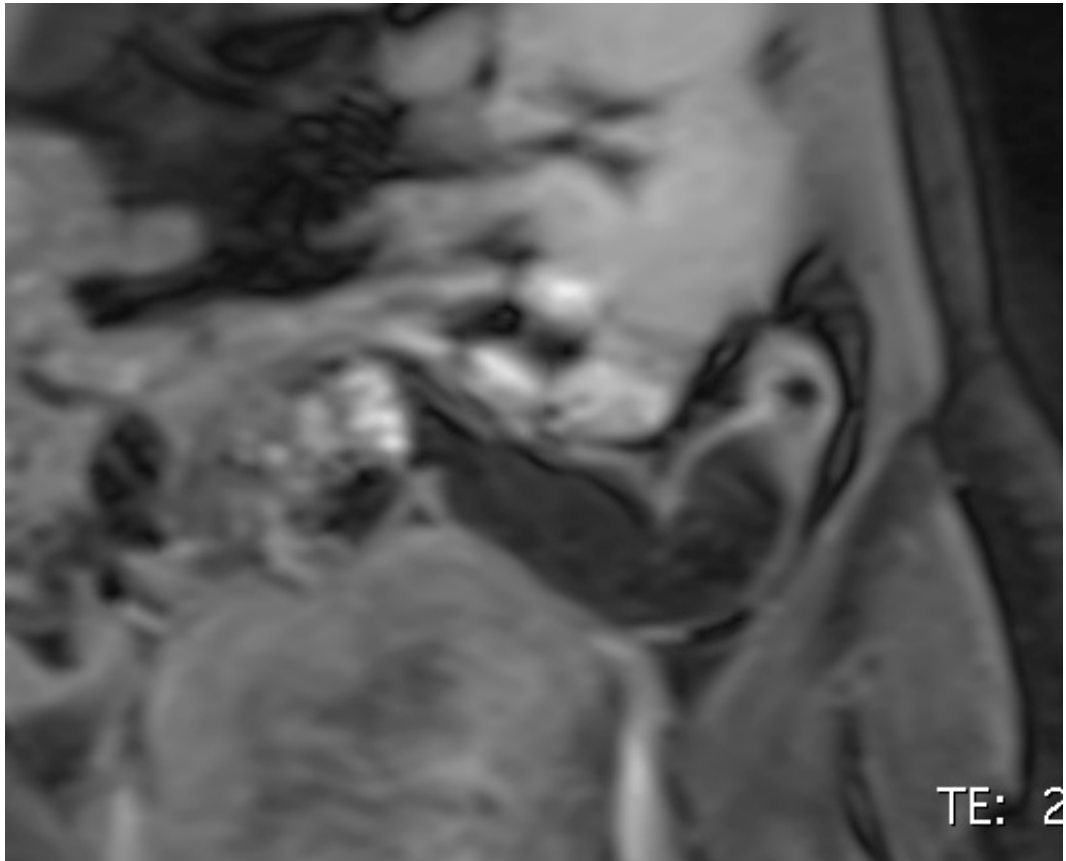


Figure 20 d: Moderate T1 enhancement of sigmoid colon with layer pattern

Score	0	1	2	3
Mural Thickness* Colon	<3mm	>3 - 5 mm	>5 - 8 mm	>8mm
Mural T2 signal**	Equivalent to normal bowel wall	Minor increase in signal-bowel wall appears dark grey on fat saturated images	Moderate increase in signal-bowel wall appears light grey on fat saturated images	Marked increase in signal-bowel wall contains areas of white high signal approaching that of luminal content
Mesenteric edema	None	Thin rim <2mm	Small pool <3 cm	Large pool >3 cm
T1 Enhancement**	Equivalent to normal bowel wall	Minor enhancement-bowel wall signal greater than normal small bowel but significantly less than nearby vascular structures	Moderate enhancement-bowel wall signal increased but somewhat less than nearby vascular structures	Marked enhancement-bowel wall signal approaches that of nearby vascular structures
Mural enhancement pattern	N/A or homogenous	Mucosal Layered		

Multiplication factor per length of segment involved by disease

Length of disease segment	0cm	0-5cm x 1	5-15cm x 1.5	>15cm x 2
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Score	0	5
Lymph nodes	Absent	Present
Comb Sign	Absent	Present

Table 27: Qualitative measurements for Qualitative MRI activity index

*measured using electronic calipers

**compared to normal small bowel

***compared to nearest vessel

MRI activity score=(Caecum score x multiplication factor for involved caecum length) + (ascending score x multiplication factor for involved ascending length) + (transverse score x multiplication factor for involved transverse length) + (descending score x multiplication factor for involved descending length) + (sigmoid score x multiplication factor for involved sigmoid length) + (rectum score x multiplication factor for involved rectum length) + score for adenopathy + score for comb sign

(Total possible score 178)

3.2.2.6.3 MaRIA index

Similarly, observations were made in six segments of colon to derive the MaRIA index using definitions proposed by Rimola et al (16, 187). The index included bowel wall thickness, mural edema (hyper intensity on T2 weighted sequence of the bowel wall relative to the signal of psoas muscle), Ulceration (deep depression in the mucosal surface of a thickened segment) and enlarged regional mesenteric lymph nodes (>1cm). Region of interest (ROI) were placed in all six segments pre contrast and post contrast (70 seconds) in the same location (Table 28) (Figure 21).

Wall thickness

ROI pre-contrast wall signal intensity

ROI post-contrast wall signal intensity

Edema Y/N

Ulcers Y/N

Table 28: MRC parameters for MaRIA index

MaRIA index = 1.5 wall thickness + 0.02 RCE+ 5 edema+ 10 ulcer

Relative contrast enhancement (RCE) was calculated as:

$$\frac{1}{4} [(WSI \text{ post gadolinium} - WSI \text{ pregadolinium}) / (WSI \text{ pregadolinium})] \times 100 \times (SD \text{ noise pregadolinium} / SD \text{ noise post gadolinium})$$

Whereas SD noise was calculated as average of three SDs of the signal intensity measured outside of the body before and after gadolinium injection.

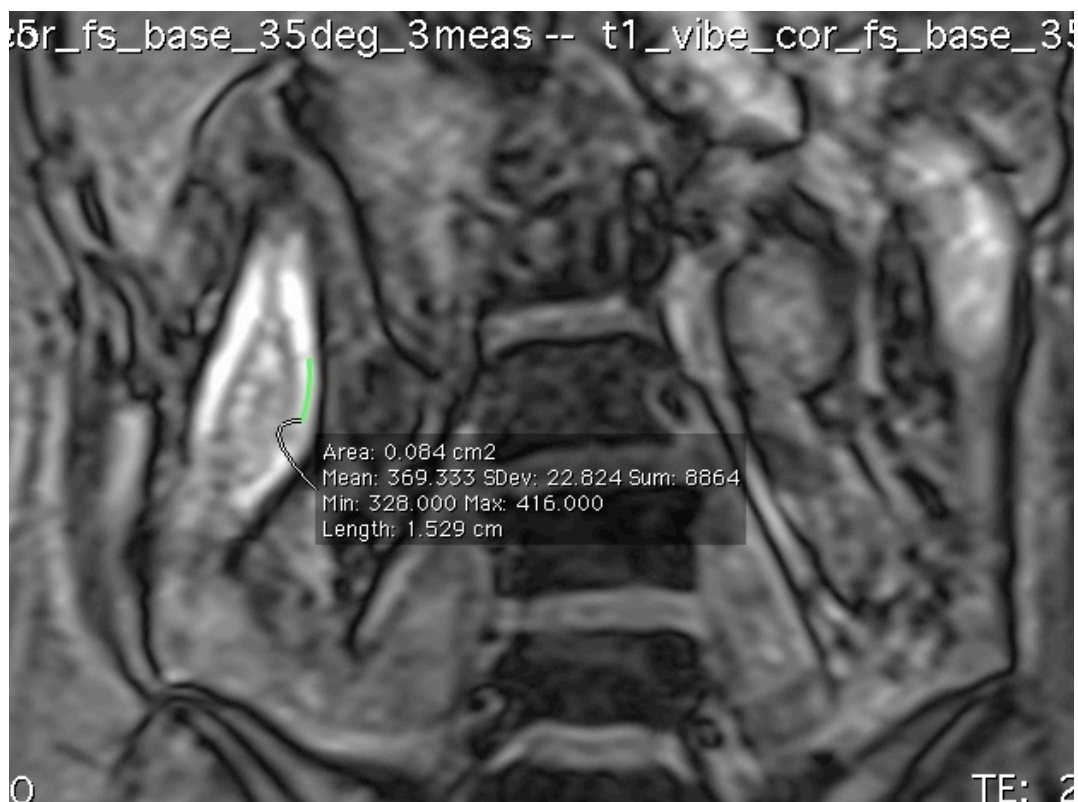


Figure 21 a: ROI – pre contrast Ascending colon

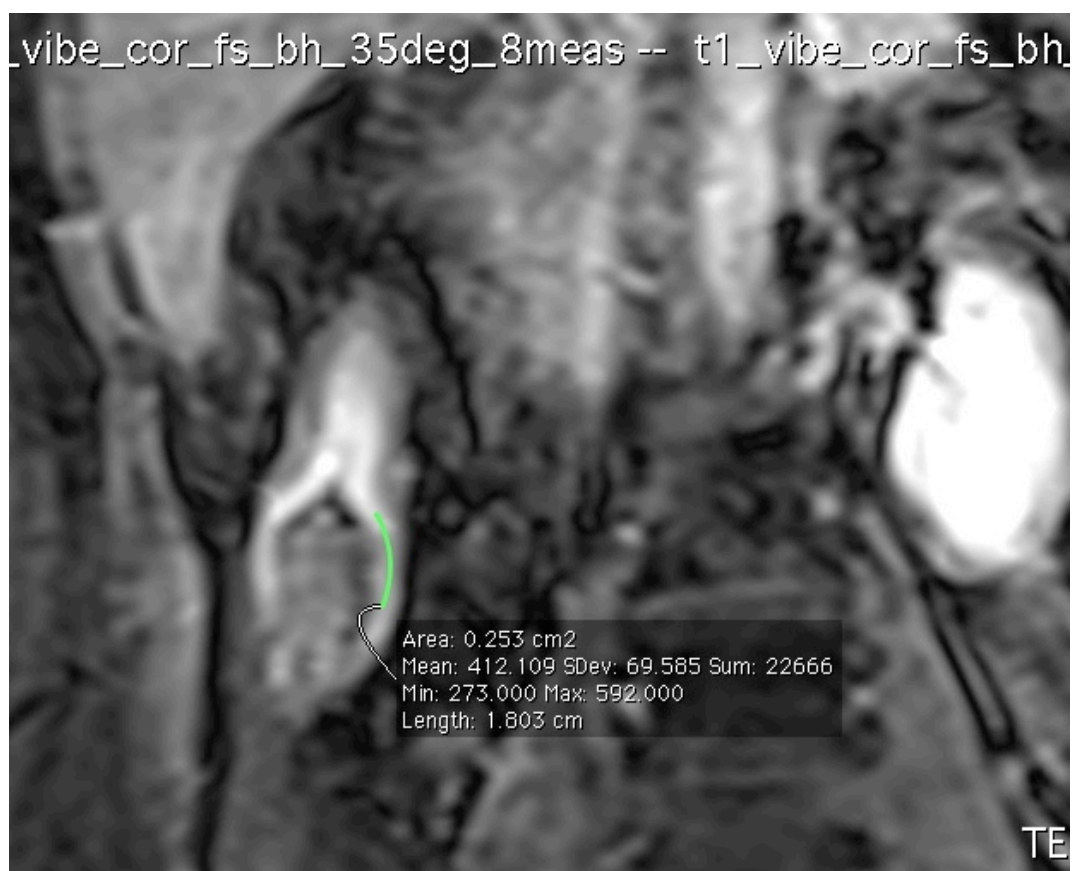


Figure 21 b: ROI post contrast – Ascending colon

3.2.2.7 Statistical analysis

Spearman correlation was used to evaluate relation between all three MRI index, CDEIS, histology grading and eAIS. This was done on a per patient basis (i.e. using total MRI, CDEIS and histology scores), and then repeated on a per segment basis (split into the 6 segments). For the MRI activity index, the scores for lymph nodes and comb sign were excluded from the individual segmental scores given the reference standard was based on luminal evaluation only.

3.2.3 RESULTS

The mean MRI index using the method of Steward was 37.53 (range 28.51 – 55.01 and SD 8.9)

The mean MRI activity score was 10.30 (range 0- 48 and SD 15.3)

The mean total MaRIA index was 6.37 (range 0- 21.81 and SD 4.0)

3.2.3.1 CDEIS

Mean total CDEIS was 5.58 with range of 0-63.6 and SD 14.64.

3.2.3.2 Histology grading and eAIS

All the biopsies taken during endoscopy were graded according to inflammation grading (1-5) in each segment with possible maximum grading of 30 in any one individual patient. The mean total histological grade was 3.7 with range of 0-12 and SD 4.092.

The mean eAIS was 3 with range of 0-12 and SD 3.569.

3.2.3.2.1 Steward score vs. CDEIS and histology scores

On per patient basis and using the total Steward score and CDEIS, there was significant correlation between the Steward score and CDEIS $r=0.559$ & $p=0.01$ but no correlation

was present with either the standard histology grading ($r=0.08$ & $p=0.71$) or eAIS ($r=0.097$ & $p=0.68$) (Figure 22).

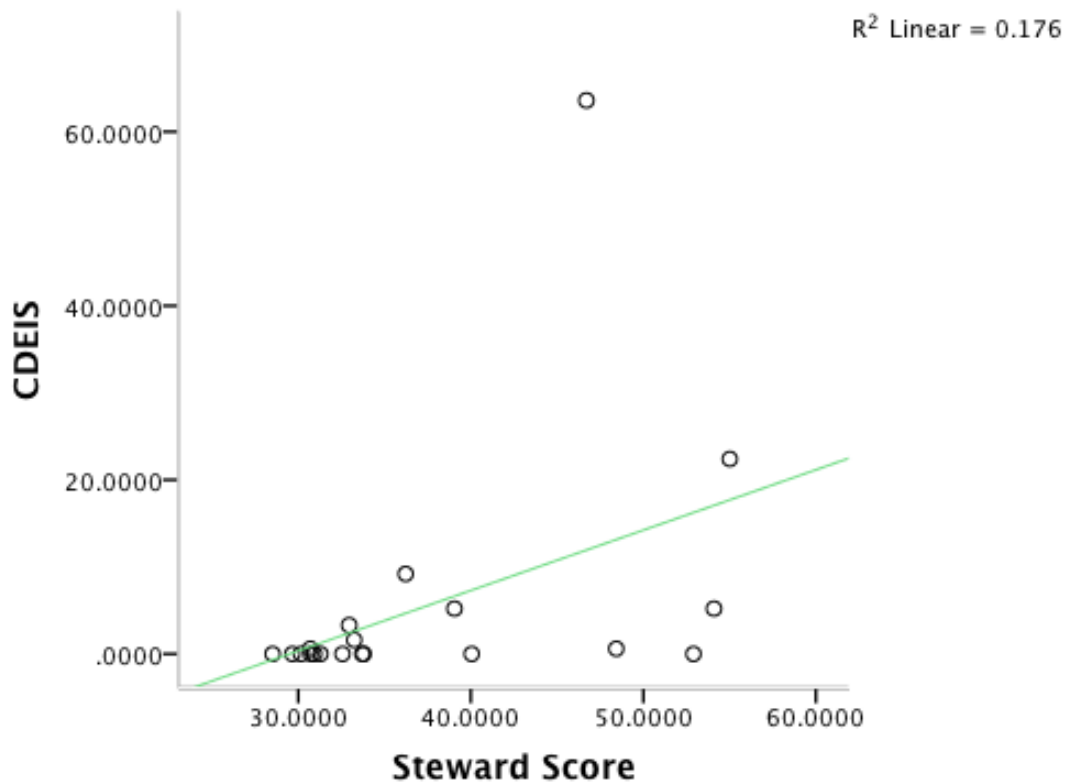


Figure 22: Scattered graph showing correlation between the Steward score and CDEIS – less than 20 points are illustrated due to overlapping of individual data points.

3.2.3.2.1.1 Per segment Data

The per segment basis mean Steward score was 8.87 and CDEIS 0.35, standard histology grading 0.62 and eAIS was 0.51. Again there was significant correlation seen between the MRI score and CDEIS ($r = 0.4$, $p < 0.01$) but no correlation was found with standard histology grading ($r = 0.098$, $p = 0.28$) or eAIS ($r = 0.11$, $p = 0.198$).

3.2.3.2.2 MRI activity score vs. CDEIS and histology scores

The MRI activity score also showed a significant correlation with CDEIS ($r=0.55$, $p=0.01$) on per patient basis, but not with histological grading ($r=0.13$ & $p=0.56$) or eAIS ($r=0.19$ & $p=0.4$) (Figure 23).

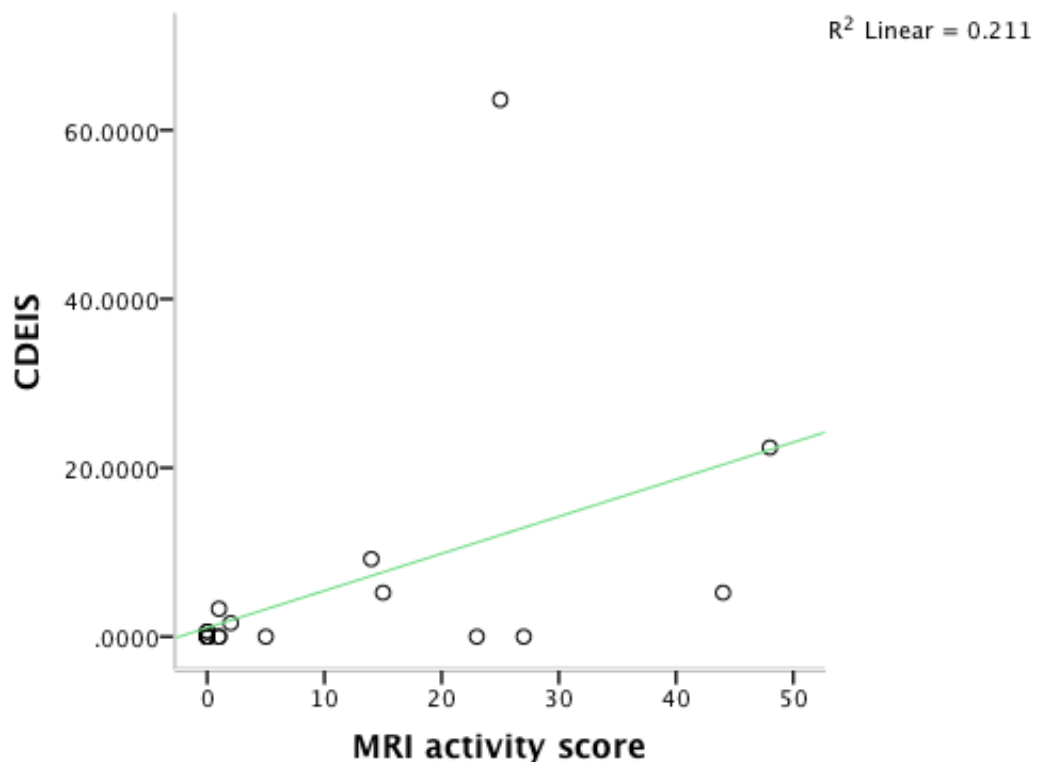


Figure 23: Scatter graph between Qualitative MRI severity index and CDEIS- less than 20 points are illustrated due to overlapping of individual data points.

3.2.3.2.2.1 Per segment data

On per segment basis the MRI activity score showed a significant correlation with CDEIS ($r=0.49$, $p<0.01$), and also histology grading ($r=0.2$, $p=0.035$) and eAIS ($r=0.22$, $p=0.02$) as well.

3.2.3.2.3 MaRIA index vs. CDEIS and histology scores

The MaRIA index showed positive correlation with CDEIS ($r=0.61$ & $p=0.005$) on per patient basis, but not with histology grading ($r=0.02$ & $p=0.93$) or eAIS ($r=0.96$ & $p=0.69$) (Figure 24).

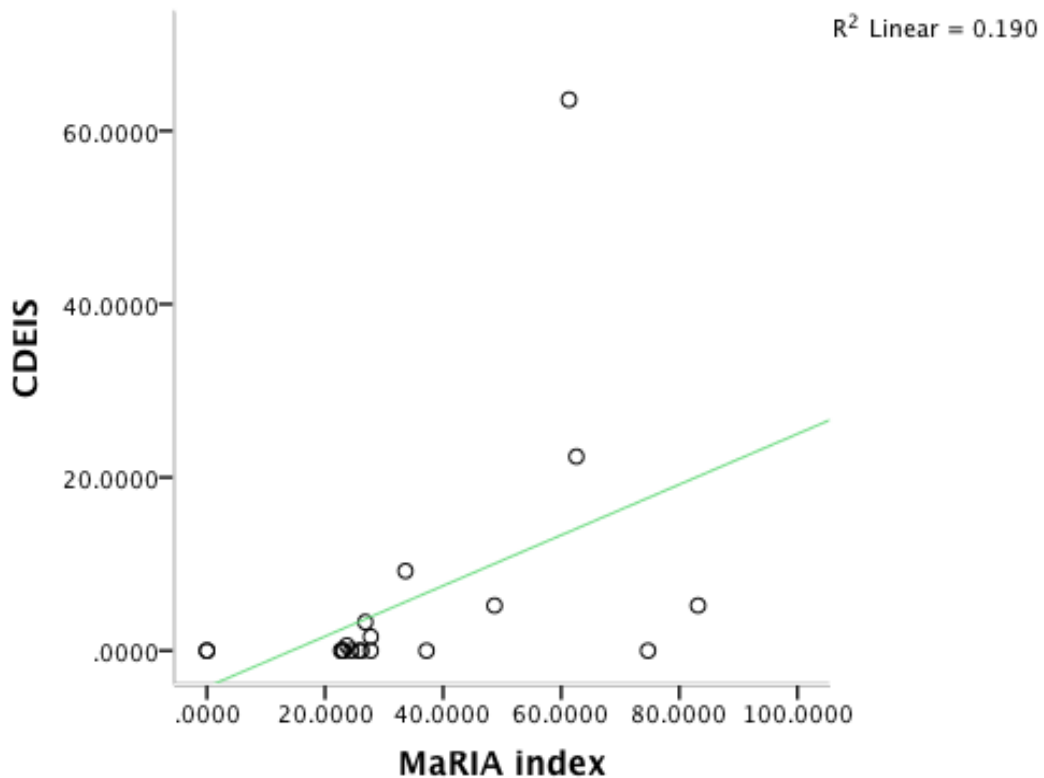


Figure 24: Scattered graph between MaRIA index and CDEIS - less than 20 points are illustrated due to overlapping of individual data points.

3.2.3.2.3.1 Per segment data

The MaRIA index also correlated with CDEIS on per segment basis ($r=0.45$, $p<0.01$) but there was no correlation found with histology grading ($r=0.16$, $p=0.1$) or with eAIS ($r=0.18$, $p=0.05$).

3.2.4 DISCUSSION

As discussed in session 1.3.3.6, MRC has emerged as a potentially useful investigation for assessment IBD related colitis but there are inconsistencies in current literature regarding techniques, MRI parameters and reference standard applied (symptoms scoring, biochemical markers, endoscopic, histological and surgical).

The study attempted to test 3 proposed MRI scores of activity against endoscopic and histological standard of reference.

The data showed that all 3 scores (Steward score, MRI activity index and MaRIA index correlated significantly with CDEIS on a per patient and per segment basis, providing some validity to their use in clinical practice.

The Steward score was based mainly on small bowel work using surgical resection specimens and (234) found wall thickness and T2 mural signal were the best predictors of inflammation : a combined score of these parameters showed a sensitivity of 81% for detection of histological inflammation. In this study I correlated the same combined score with histological sampling from the colon and failed to re-produce this positive correlation. That in general MRI scores did not correlate well with colonic histology (excepting the MRI activity index on a per segment basis) is perhaps to be expected.

Histological biopsies are prone to sampling error, and grading is subjective.

Furthermore although the study attempted to match sites of MRI and histological sampling on a segmental basis, in reality the actual anatomical matching would likely have been poor. It is easier to match MRI with histology in the terminal ileum given the

landmark of the ileocaecal valve, then in the colon where even segmental demarcation is subjective.

The MRI activity score is a modification of Steward score, and previous work has shown significant correlation with faecal calprotectin level (Kendall's tau $b=0.42$, $p=0.0009$). Contrary to Steward score, this score was significantly correlated with both histology grades on per segment basis. It is of interest that the MRI activity index seemed to best correlated with the reference standard overall (i.e. CDEIS and histology). The score takes into account many more parameters than the Steward score and MaRIA index, including the length of the bowel affected in each segment. This presumably added to its ability to assess colonic inflammatory activity. However it is clearly more complex than the others scores to collate and how useful it is in time pressured day to day clinical practice is debatable.

The Rimola score (including wall thickness, contrast signal intensity and RCE) has been shown to correlate well with endoscopic inflammation severity. The present study was able to reproduce this work: MaRIA showed positive correlation with CDEIS, although again no such association was found against histological features of inflammation.

The MRI parameters, which make up the scores, are of interest. An assessment of wall thickness and T2 signal was common to all 3 systems, with inclusion of contrast enhancement in the MRI activity score and MaRIA. The strength of correlation with CDEIS (on a per patient basis) was not overtly less with the simple Steward score in comparison to the more complex MRI activity score and MaRIA score. This perhaps suggests grading contrast enhancement may not be crucial in predicting disease activity. In chapter 3.1 I have already shown that there are segmental differences in contrast uptake in normal colon, and the work of Taylor et al (154) has shown contrast uptake is related to disease chronicity and microvessel density and not just inflammatory activity.

However other workers have previously included contrast uptake in their score. Notably Ajaj et al (15) used an MRC score based on (contrast uptake, wall thickness, haustral folds and peri focal lymphnodes) and in comparison with endoscopic biopsies found positive results for detection of IBD (sensitivity of 87% and specificity of 100). Like the present study, they used a dark lumen technique.

Furthermore, as I present in later chapters (3.4), quantitative measurement of contrast enhancement does correlate with disease severity in acute severe colitis, so overall it I think we can conclude that it is of value. It does seem however that wall thickness and T2 signal (likely reflecting mural edema) are the best predictors of disease activity.

The present study utilized a full bowel preparation and dark lumen technique Scheryer et al (189) used a bright lumen technique while Langhorst et al (181) made use of fecal tagging. However neither found such positive results for detection of inflammatory changes. The present study does therefore also support the concept that a dark lumen technique after bowel purgation is “state of the art” for MRC.

Other MRI sequences are also now under investigation. Ossalah et al (183) have assessed disease activity with help of diffusion weighted imaging using a score based on DWI hypersensitivity, contrast enhancement pattern, bowel thickening, parietal edema and presence of ulcers. They found good correlation with an endoscopic reference standard. The present study did not utilize diffusion weighted imaging. However I consider this technique in the assessment of acute severe colitis (Chapter 3.4).

The findings of this study should be interpreted with some caution. The cohort included a mixture of patients with UC and CD. This was mainly for pragmatic reasons- recruitment of patient under going colonoscopy to undergo an additional MRC was challenging. The number in each group precludes meaningful sub analysis of correlation

with the endoscopic and histological scores, but it is possible the MRI parameters, which best correlate with clinical indices of inflammation will differ between patients with UC and CD.

The MRI scoring was done by two research fellows rather than consultant radiologists, however, the scoring was closely monitored by the supervising radiologist, although a formal assessment of agreement between the observers and the radiologist would have been useful. Finally, several of the recruited patients had low level of activity and attracted zero scores. Although the statistical testing performed concurred with medical statistician advice, it is acknowledged that datasets with several zero scores may artificially increase correlation coefficients. A formal power calculation was not performed and it is possible the study was underpowered. Clearly a larger dataset is required containing patients with more active disease to test in conclusion, and this data can be used to inform calculation of an appropriate sample size for such a future study.

In summary in this relatively small exploration study, all three qualitative MRI indices correlated with an endoscopic score of disease severity – CDEIS which itself is gold standard for endoscopic disease assessment. This suggests MRC assessment of disease activity is a viable proposition in clinical practice as a complementary tool in cases of incomplete colonoscopy but perhaps as an alternative to colonoscopy as a first line test. As later presented in chapters 4.1 & 4.2, patient experience of MRC and colonoscopy is an important consideration, but on diagnostic accuracy criteria, MRC performs well in assessing disease activity.

3.3 QUANTITATIVE MEASUREMENTS OF THE BOWEL WALL CHARACTERISTICS IN ACUTE COLITIS

3.3.1 INTRODUCTION

Assessment of disease severity, accurate monitoring of response to medical treatment and prediction of treatment failure are very important in management of acute colitis and its complications as discussed in chapter 3.3.

In the previous chapter, I concentrated on a qualitative scoring system (TCIS) based on subjective assessment of T2 weighted images by reporting radiologists. This was successful, showing good correlation with clinical parameters and potentially acting as a new prognostic tool. Although I was able to demonstrate good interobserver agreement with the qualitative scoring system, in reality any score that relies upon the opinion of the reporting radiologist is subjective and at risk of observer bias. Furthermore I did not consider contrast enhancement in the tested score, which as we have seen likely does have utility. The use of diffusion-weighted imaging was also not considered.

In this next study, I apply quantitative measurements via ROI placement in the same patient cohort described in the previous chapter. Considered sequences include dynamic contrast enhanced T1 weighted images, diffusion weighted images as well as T2 weighted data.

If MRI can reliably quantify disease severity in acute colitis and rapidly detect changes in response to therapy, it could have a useful role in informing clinical management decisions, providing more objective measurement of clinical progress.

The aim of this study is to establish if quantitative MRI mural parameters correlate with clinical markers of inflammation and to assess changes in these parameters in response to therapeutic intervention.

3.3.2 MATERIAL AND METHODS

Twenty one patients recruited for previous study (Chapter 3.3) were also included in this study. Patient demographics have been described in detail in section 3.2.2. All these patients were admitted to hospital (UCLH) with acute colitis and satisfied the inclusion criteria of acute colitis of Truelove and Witt's. 14 patients had an unprepared MRI within 48 hours of admission and 18 within 72 hours of admission while remaining 3 patient had MRI after 5, 7 and 9 days respectively. They were started on medical therapy as described in table 31. As part of clinical assessment a daily stool chart was maintained and CRP level was checked regularly after initiation of medical therapy. These two clinical markers were used to calculate the fulminant clinical index FCI, which has been previously used as a predictor in clinical trials (250).

$$FCI = \text{Stools} + 0.14 \times \text{CRP}$$

A repeat MRI was performed at a median of 5 days (range 3-7) after first MRI in fourteen patients.

3.3.2.1 MRI protocol

All patients were fasted for two hours prior to MRI and they all had intravenous spasmolytic Buscopan 0.3mg/kg (maximum 20 mg). Images were acquired in the prone position with a 1.5T Siemens Avanto (Avanto; Siemens, Erlangen, Germany) magnet using the body and spine array coils.

- A coronal and axial Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) of abdomen and pelvis
- Axial and coronal T2 weighted dual spin Echo (T2 quantitation)
- Coronal free-breathing echo planar diffusion weighted images (EPI-DWI) with incrementing 'b' values (0,50,200 and 400).
- Pre – contrast three breath-hold coronal fat saturated 3D Fast Low Angle Shot (FLASH) images of the abdomen and pelvis with different excitation flip angles (flip angles 5°, 10°, and 35°) (table 23)
- Prior to intravenous contrast administration, three 3D FLASH baseline sets of coronal images were acquired during suspended inspiration
- A single dose of (0.2 mg/Kg) IV gadoterate meglumine (Dotarem; Guerbet Roissy, France) was then injected into an arm vein at 3 mL/sec, followed by a saline chaser (10 mL).
- At injection the patient was asked to hold his/her breath for 20 seconds (during which a single 3D FLASH volume dataset was acquired), followed by 10 seconds of gentle breathing, immediately followed by another 20 seconds breath hold acquisition and 10 seconds of gentle breathing. The acquisition protocol was repeated to generate a total of 8 post contrast 3D FLASH datasets.

\

	HASTE	EPI-DWI
FOV	Variable*	HASTE matched
Slices	19-27	19-27
Stacks	1-2	1
TR (ms)	1200	7900
TE (ms)	52	82
Matrix	256x196	192x154
Slice thickness (mm)	4	4
Interslice gap (mm)	5.2	5.2
Averages	4	1
Echo train	256	n/a
iPAT	2	2
‘b’ value	n/a	0,50,200,400

*to encompass patient anatomy

Table 29: MRI protocol

3.3.2.2 Data Analysis

Data analysis was performed on Images using open source OsiriX medical imaging platform (<http://www.osirix-viewer.com>) as described in section 3.1.2.3 and 3.2.2.6 by thesis author (Rehana Hafeez) after dividing colon into six segments. Single freehand linear Regions of Interest (ROIs) were located in the colonic wall of all six segments on the T2 weighted, T1 weighted and diffusion weighted images as detailed below. In case of fourteen patients who had a repeat scan after medical treatment ROIs were placed carefully to match those placed pre treatment.

3.3.2.2.1 T2 weighted images

Pre treatment and post treatment ROIs were placed on T2-HASTE coronal fat saturated images in each of the 6 colonic segments. The mean ROI signal intensity (SI) was recorded for each of six segments in every patient. Average T2 signal intensity and Maximum T2 values for each patient were recorded. A single CSF- ROI was also placed in each patient and ratio between Av T2 and CSF SI was calculated (Figure 38).

3.3.2.2.1 T1 weighted images

Pre treatment ROIs were placed on T1 weighted images both pre contrast and post contrast in the 21 patients pre treatment and 14 patients had post treatment. As detailed in section 3.1.2.4, the signal from the three pre-contrast baseline acquisitions for a given ROI was averaged, provided a single pre –contrast ROI signal intensity for each colonic segment. T1 was calculated for each segment and at each of the 8 post contrast time points in Microsoft Excel for Mac (2011) using the expression for the evolution of signal intensity in spoiled gradient echo and solving for T1 (230). The T1 relaxation rate (R1) was derived by $1/T1$ (Figure 25).

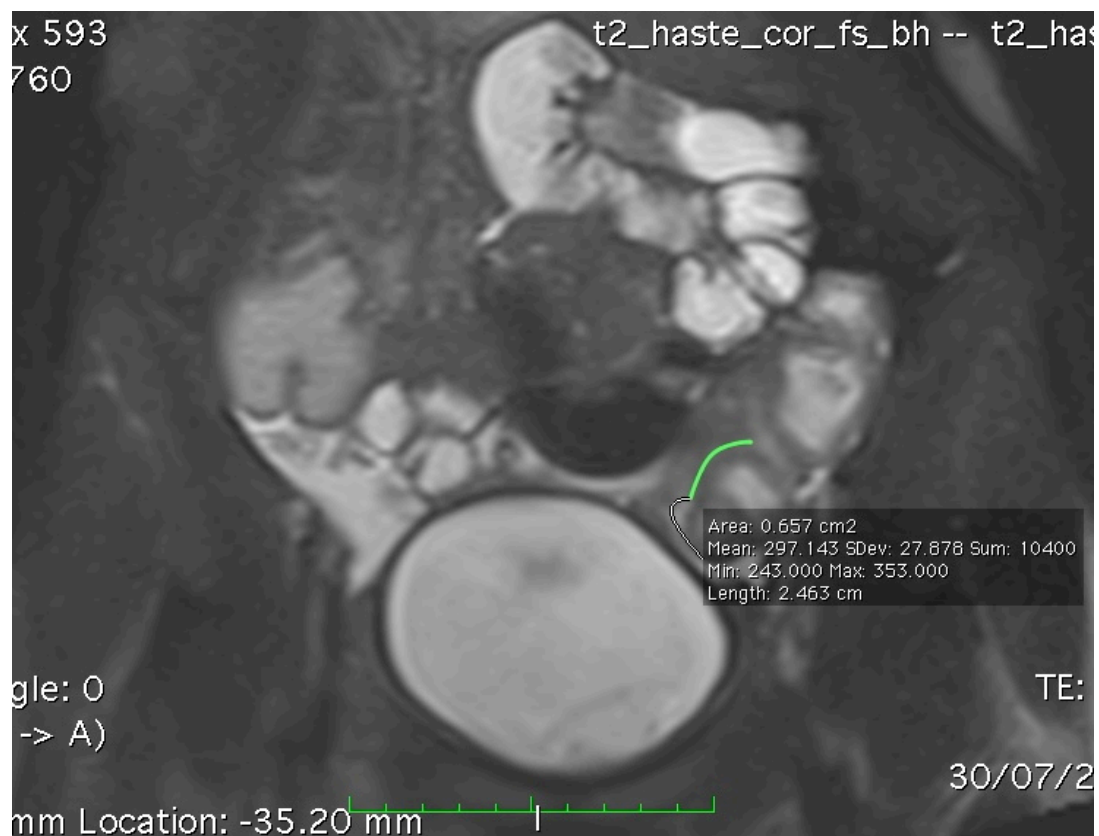


Figure 25 a & b: Pre treatment and post treatment T2- ROI

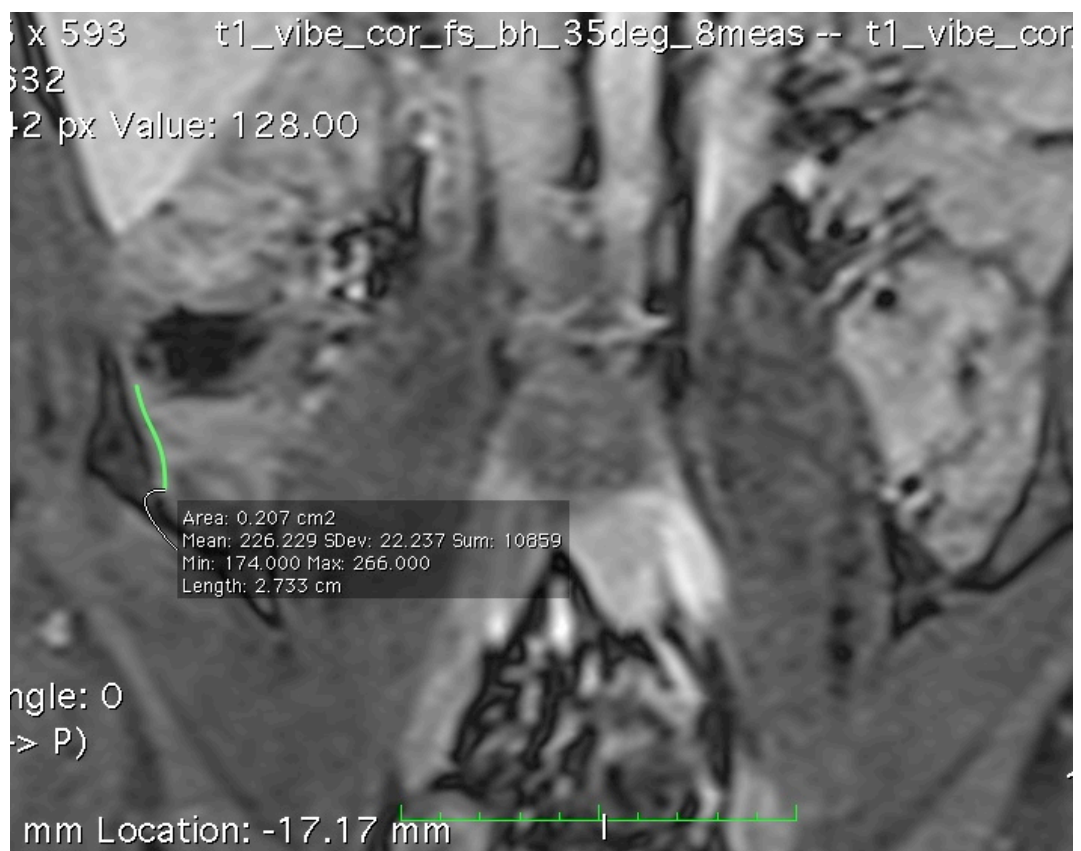
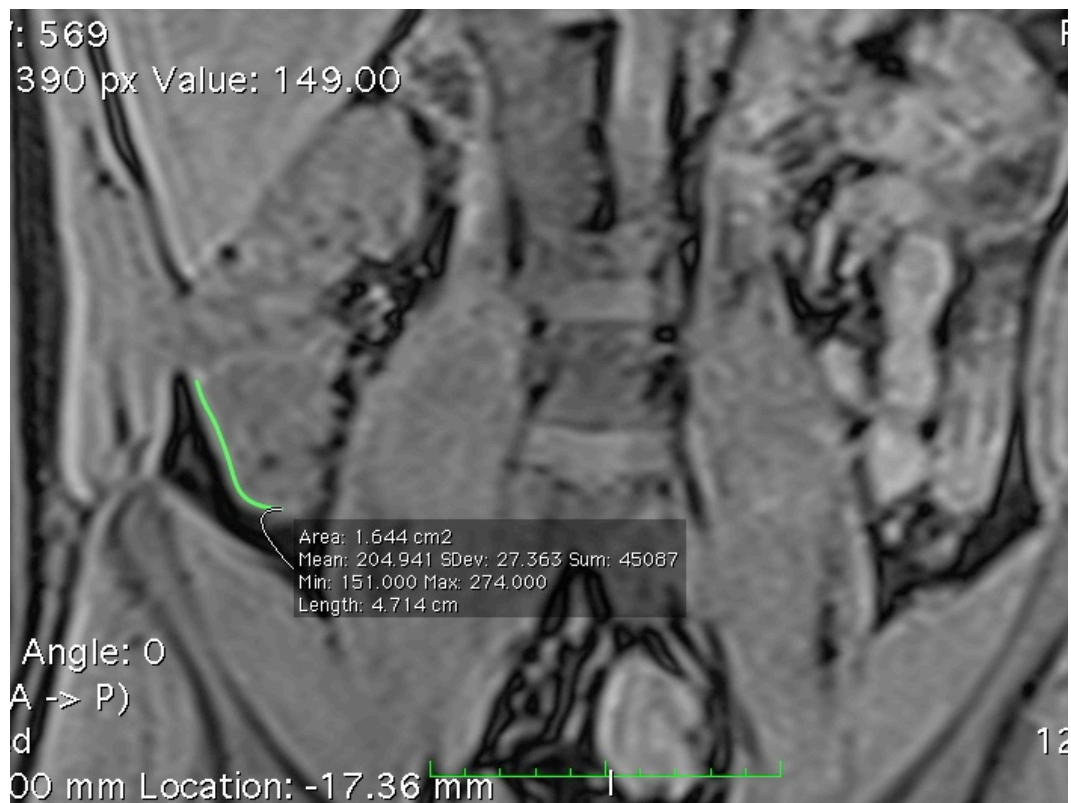


Figure 26: ROIs-Pre treatment pre contrast P0 (a) post contrast P3 (b)

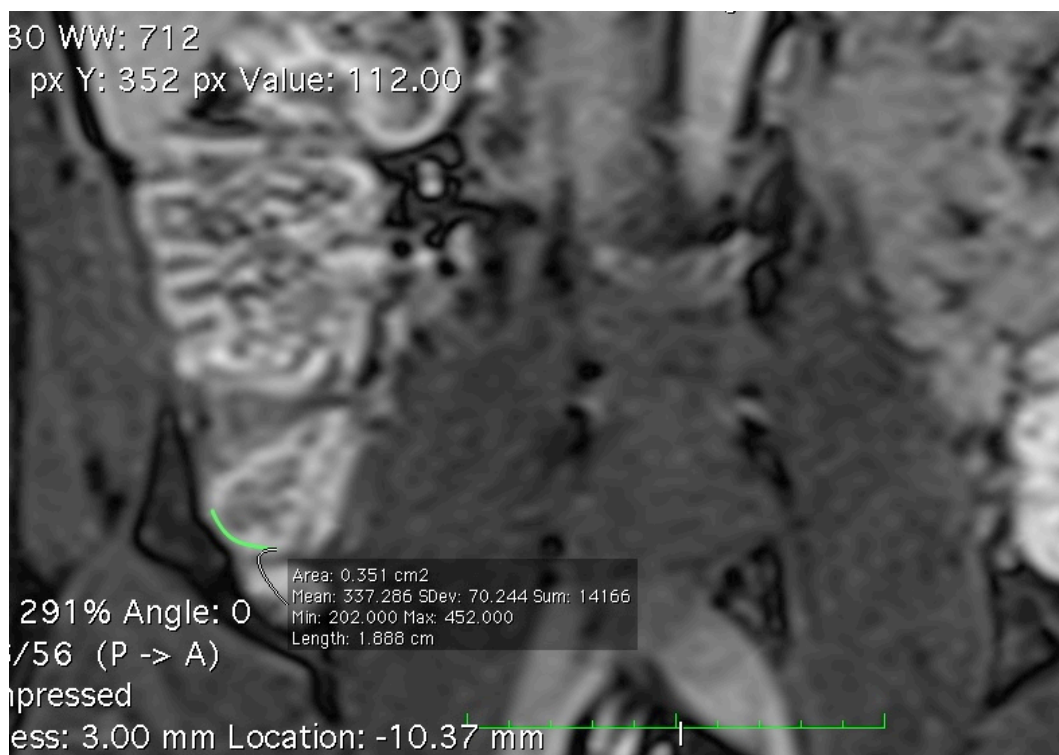
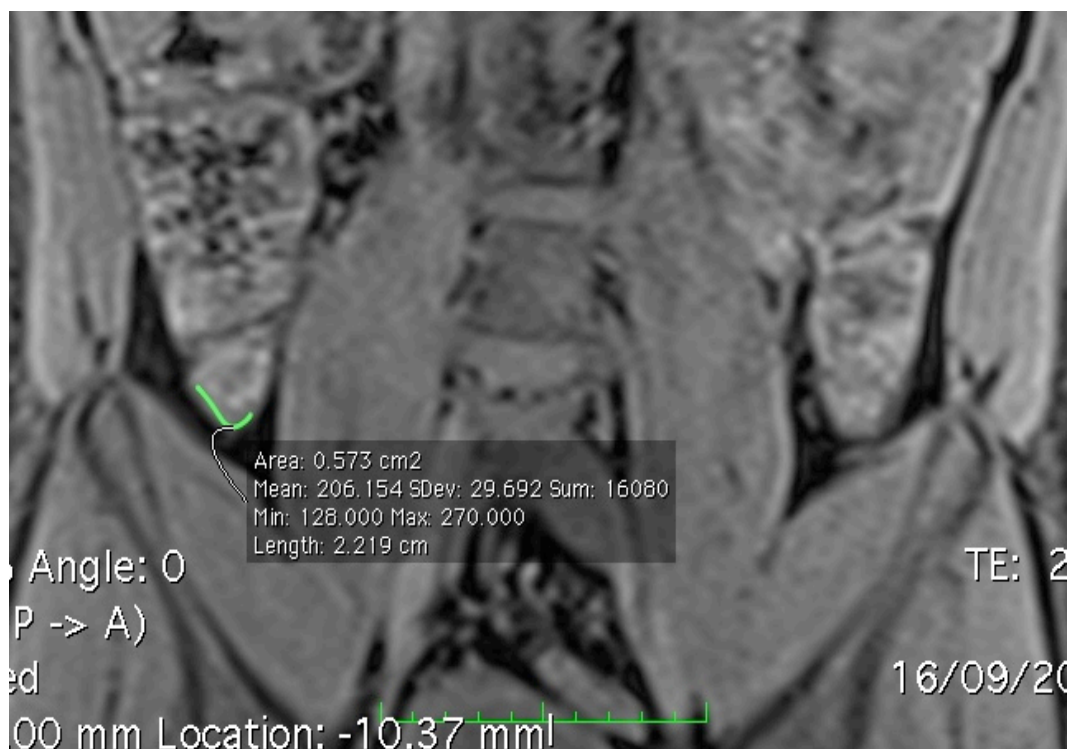


Figure 26 c & d: Post treatment P0 and P3

3.3.2.2.2 Diffusion weighted images

Full diffusion weighted image datasets were available in 18 patients pre treatment, and 13 post treatment. Single mural ROIs were placed in abnormal colonic segments after review of T2 weighted images. The average signal intensity from each ROI was recorded and apparent diffusion coefficient (ADS) was calculated by exponential fitting to the 4 increasing 'b' value signal intensities using a standard least squares regression model incorporated in Microsoft excel.

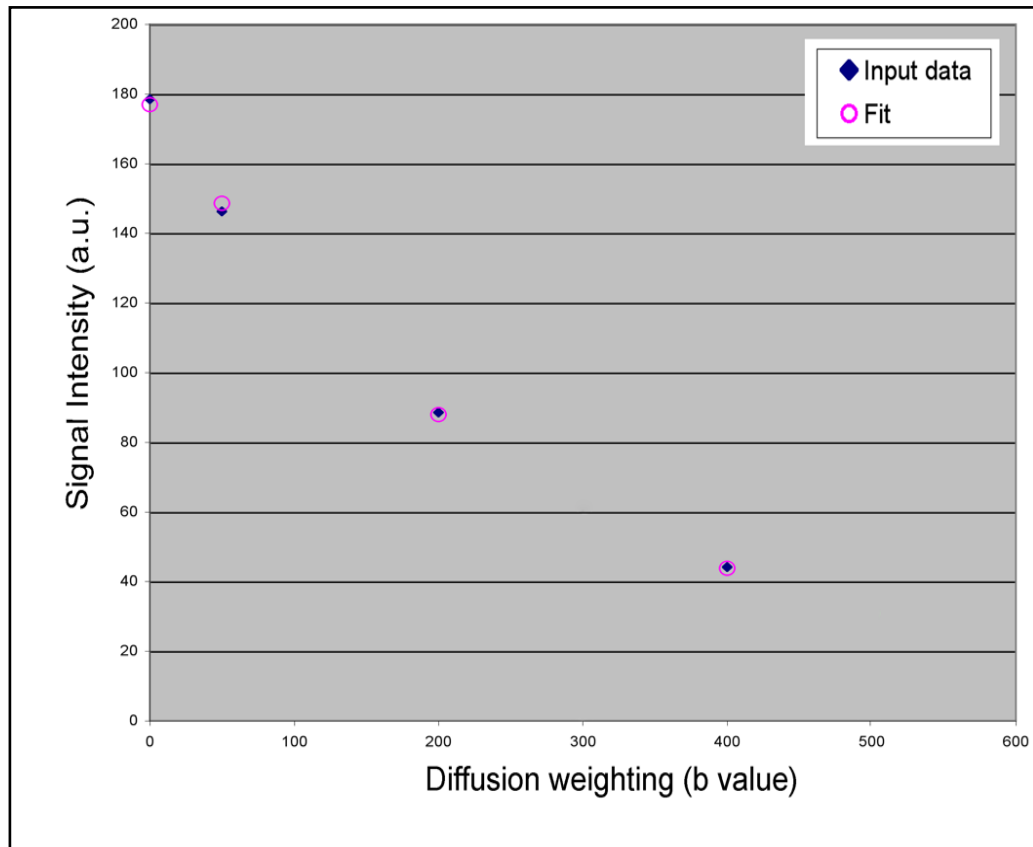


Figure 27 a: Calculation of ACD by exponential fit of ROI signal intensity

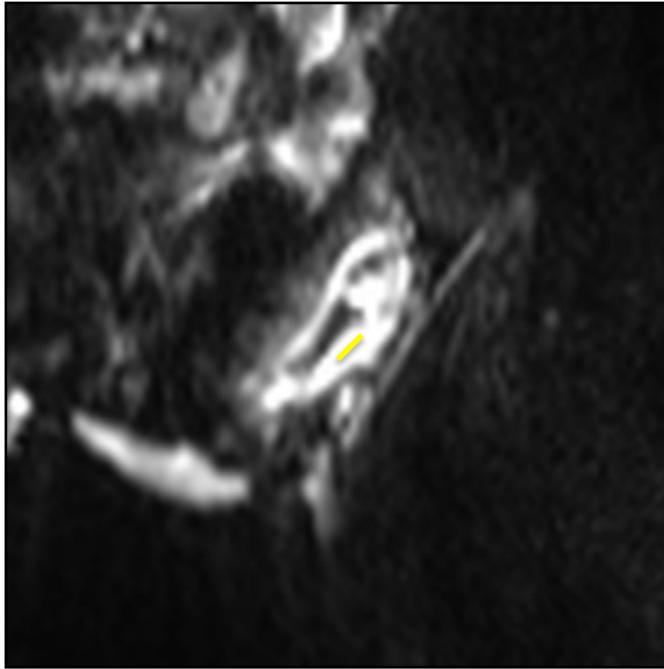


Figure 27 b:
ROI Sigmoid
colon b0

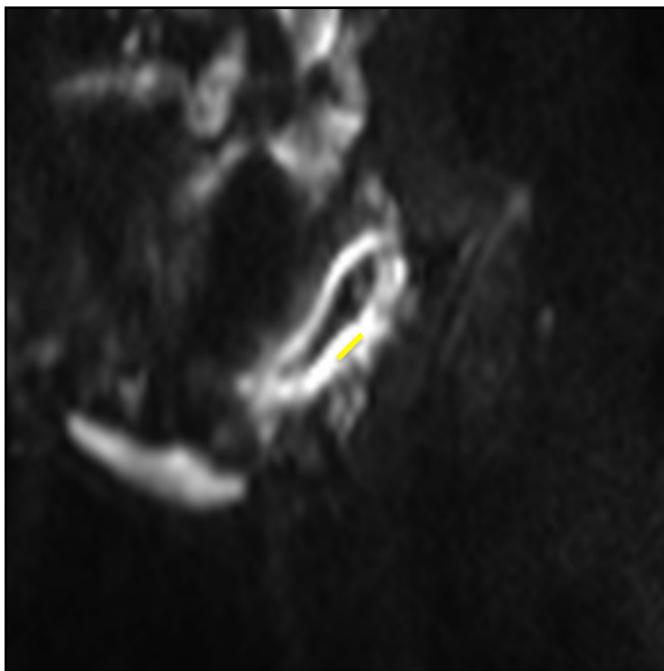


Figure 27 c:
ROI- sigmoid
colon b50

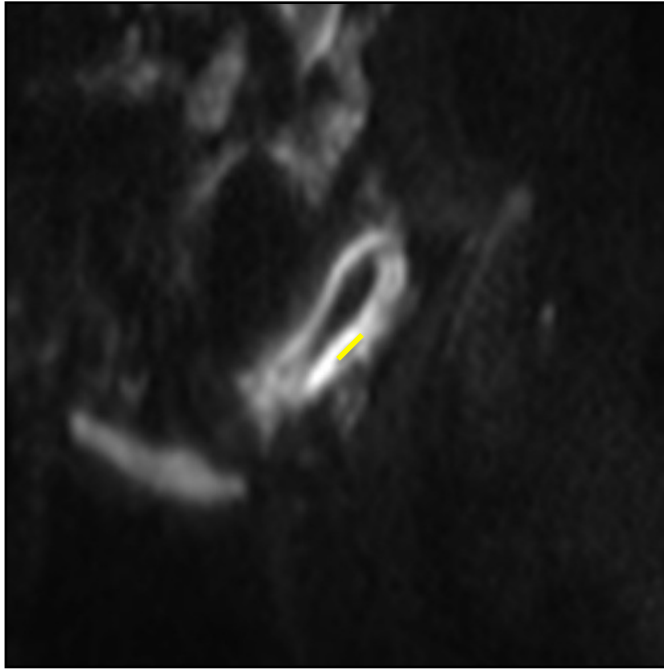


Figure 27 d:
ROI- sigmoid
colon b200

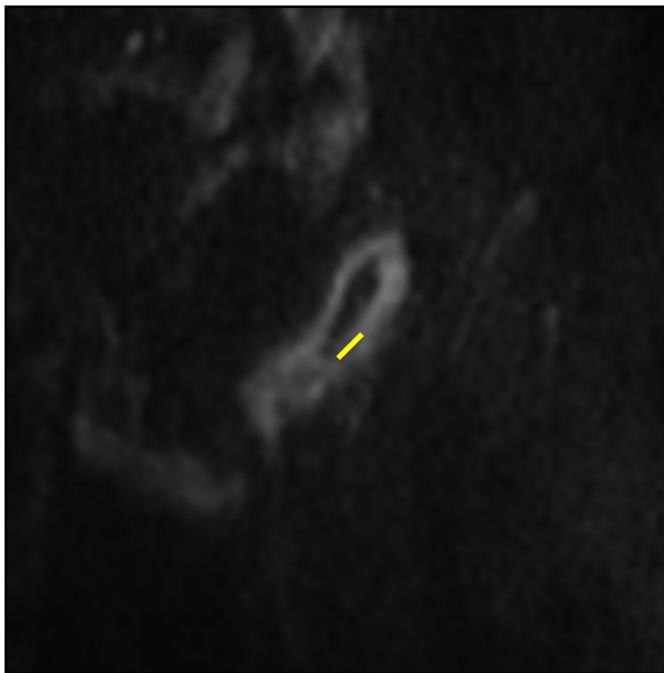


Figure 27 e:
ROI-sigmoid
colon b400

Figure 27 b-e: Sigmoid colon ROI's on diffusion weighted imaging

3.3.2.3 Statistical Analysis

The MRI quantitative parameters were compared with the fulminant colitis index (FCI) before and after the treatment by using spearman rank correlation.

In particular an average colonic T2 signal, maximum segmental T2 signal and ratio between T2 and CSF intensities were calculated for each patient. In addition based on the enhancement curves generated in normal colon (chapter 3.1), time point P3 post contrast was taken to represent the peak of contrast enhancement. The pre contrast (P0) R1, P3 R1 and P3-P0 R1 were calculated. The average and maximum colonic ADC was also calculated for correlation with the FCI

MRI parameters were compared before and after treatment by using the paired t test.

3.3.3 RESULTS

Pre treatment and post treatment CRP and stool frequency was used to calculate a clinical index –

FCI pre treatment= 16.65 (range 8.24-32.19)

FCI post treatment= 8.43 (range 3.7-16.96)

3.3.3.1 Correlation between FCI and T2 weighted imaging

FCI was not significantly correlated with Average T2 signal, Maximum T2 segmental signal or T2/CSF ratio (Table 30).

	FCI	Av T2	Max T2	T2/CSF
Pre treatment (n)	16.65	309.366	456.211	0.4097
	(21)	(21)	(21)	(21)
Correlation		r= -0.133203	r=0.051	r=0.155296
		p=0.5618	p=0.826	p = 0.4983
Post treatment (n)	8.43215	259.140	361.511	0.14558
	(13)	(13)	(13)	(13)
Correlation		r=0.028	r=0.203297	r= -0.120879
		p=0.928	P = 0.4935	P = 0.4935

Table 30: Pre and post treatment correlation between FCI, Av T2, max T2 and T2/CSF

3.3.3.2 Correlation between FCI and T1 weighted imaging

No correlation was found between FCI and Average pre contrast R1 (P0) and post contrast R1 (P3) (table 39) However there was a significant correlation between (P3-P0) and FCI. Post treatment both pre (P0) and post contrast (P3) R1 correlated with FCI but not P3-P0.

	FCI	P0 R1	P3 R1	P3-P0 R1
Average Pre treatment (n)	16.65	367.781	196.065	163.241
	(18)	(18)	(18)	(18)
Correlation		r=0.420	r=0.240491	r=0.581612
		p=0.074	P =0.3467	P = 0.0126
Average Post treatment (n)	8.432	285.791	159.893	125.898
	(13)	(13)	(13)	(13)
Correlation		r=0.634	r=0.872	r=0.427
		p=0.049	p=0.001	p=0.219

Table 31: Pre and post treatment correlation between FCI, Av P0 R1, Av P3 R1 and P3-P0 R1

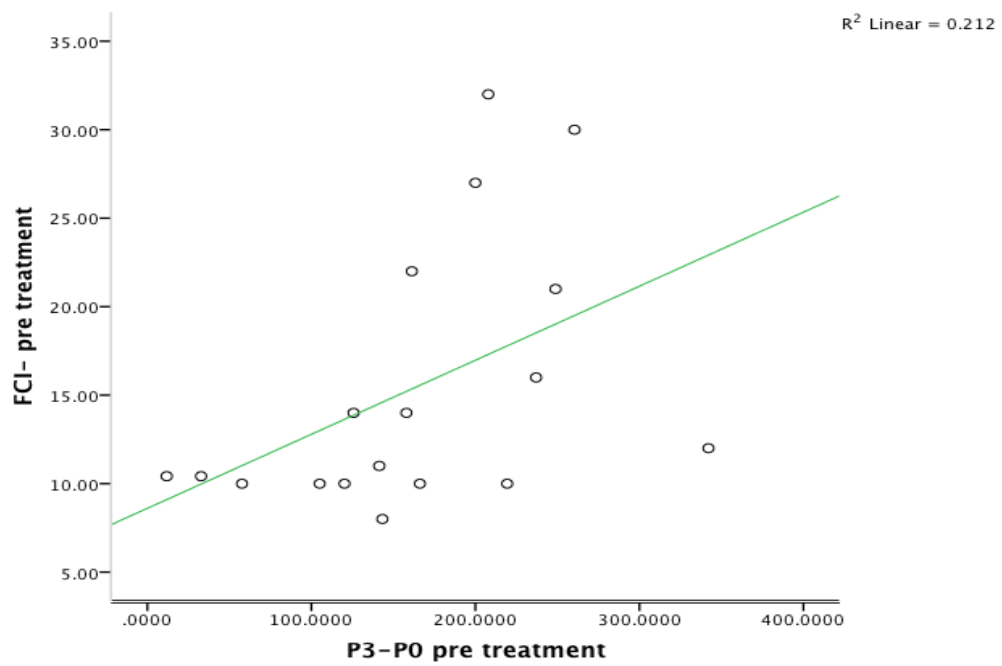


Figure 28: scattered graph between pre treatment FCI and P3-P0 R1

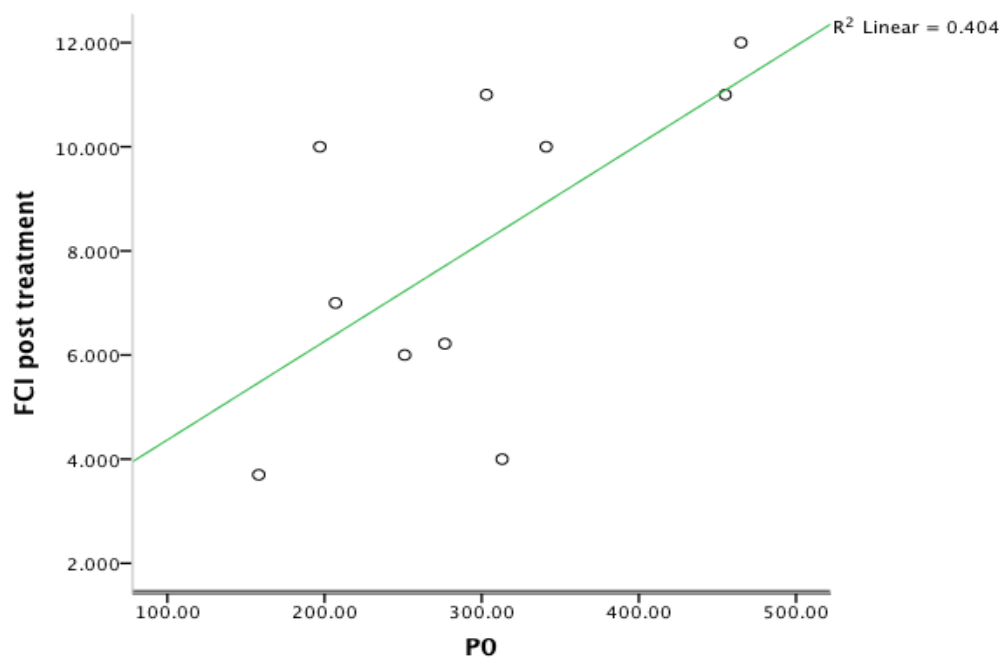


Figure 29: scattered graph between FCI and pre contrast (P0) R1 after medical treatment

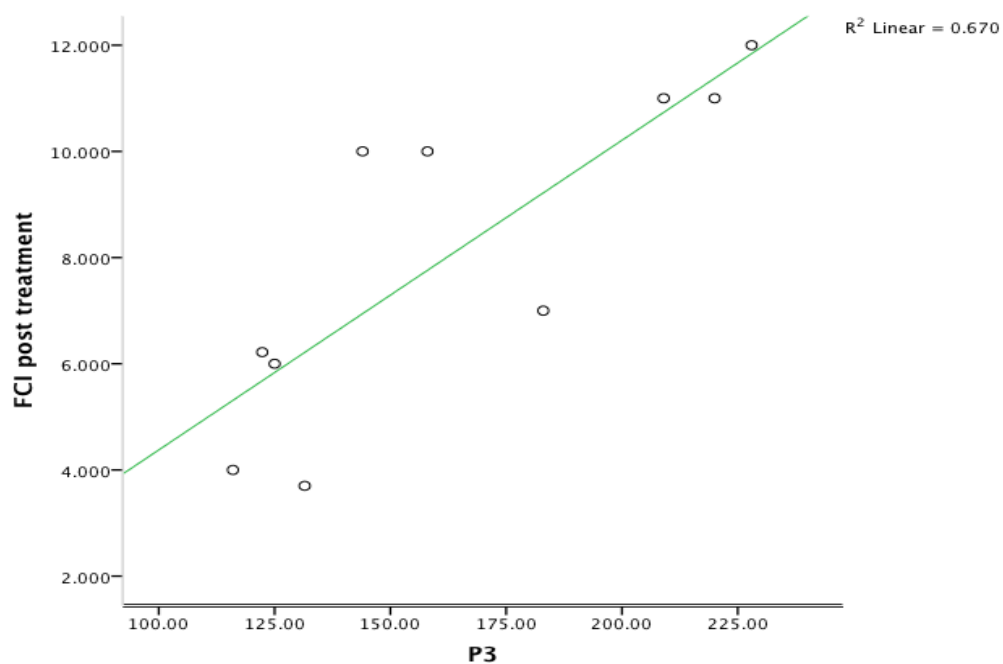


Figure 30: post treatment scattered graph between FCI and P3 R1

3.3.3.3 Correlation between FCI and Diffusion weighted imaging

Average ADC and maximum ADC value was calculated for each patient (18 pre treatment and 13 post treatment). No significant correlation was found between FCI and ADC value (Average or Maximum) before or after medical treatment.

	FCI	Av ADC	Max ADC
Pre treatment	15.6	0.001610	0.003572
(n)	(18)	(18)	(18)
Correlation		r=0.321	r=-0.080
		P = 0.194	P = 0.752
Post treatment	8.432	0.001260	0.002777
(n)	(13)	(13)	(13)
Correlation		r=-0.453	r= -0.384615
		p=0.121	P = 0.195

Table 32: Pre and post treatment correlation between FCI, Av ADC and max ADC values

3.3.3.4 Change in MRI quantitative parameters after medical therapy

There was significant difference in Av T2 values before and after the treatment in the 14 patients who has repeat MRI (Mean of difference = 58.824, SD = 59.415, SE= 15.879, 95% CI= 24.519 to 93.129 and p=0.003). Similarly, Max T2 fell significantly after treatment (Mean difference= 115.087, SD= 165.60, SE= 44.259, 95% CI= 19.470677 to 210.704466 and p= 0.02). However, the T2/CSF ratio was not significantly different (Mean difference= 0.0419, SD= 0.1201, SE= 0.032, 95% CI= -0.027467 to 0.111329 and p= 0.21). There was no change in either Av or max ADC after treatment (p=0.85 and p=0.24 respectively).

Pre contrast R1 decreased after medical therapy (Mean diff 121.960, SD= 96.78, SE= 29.182, 95% CI = 56.939 to 186.98 and p=0.002), post contrast R1 at P3 also decreased significantly (Mean diff 79.091, SD=84.832, SE=28.277, 95% CI= 13.883 to 144.299 and p=0.023) and similarly there was significant difference in P3-P0 R1 after treatment (Mean diff 55.137, SD=66.699, SE= 21.092, 95% CI= 7.4233 to 102.850 and p =0.028).

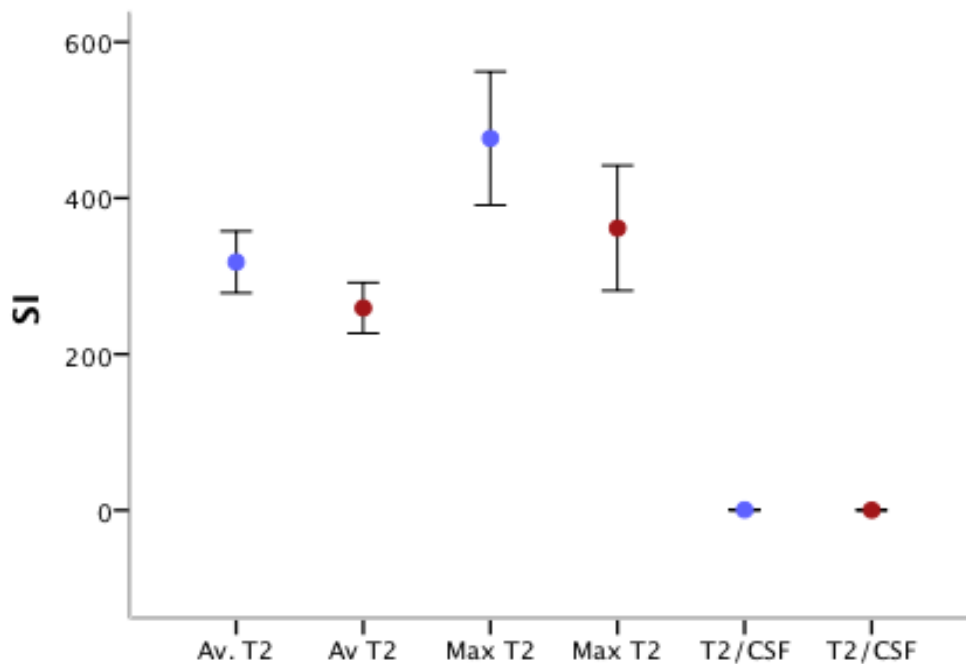


Figure 31: AvT2, Max T2 and T2/CSF before and after treatment (with 95% CI).

Pre treatment ● Post treatment ●

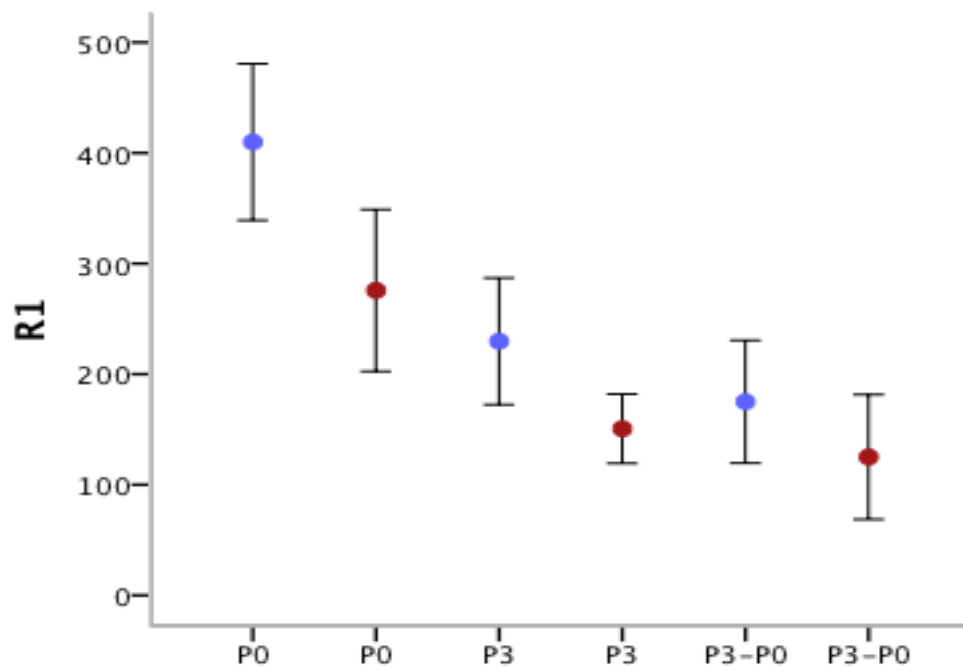


Figure 32: P0, P3 and P3-P0 before and after medical treatment (with 95% CI)

Pre treatment ● Post treatment ●

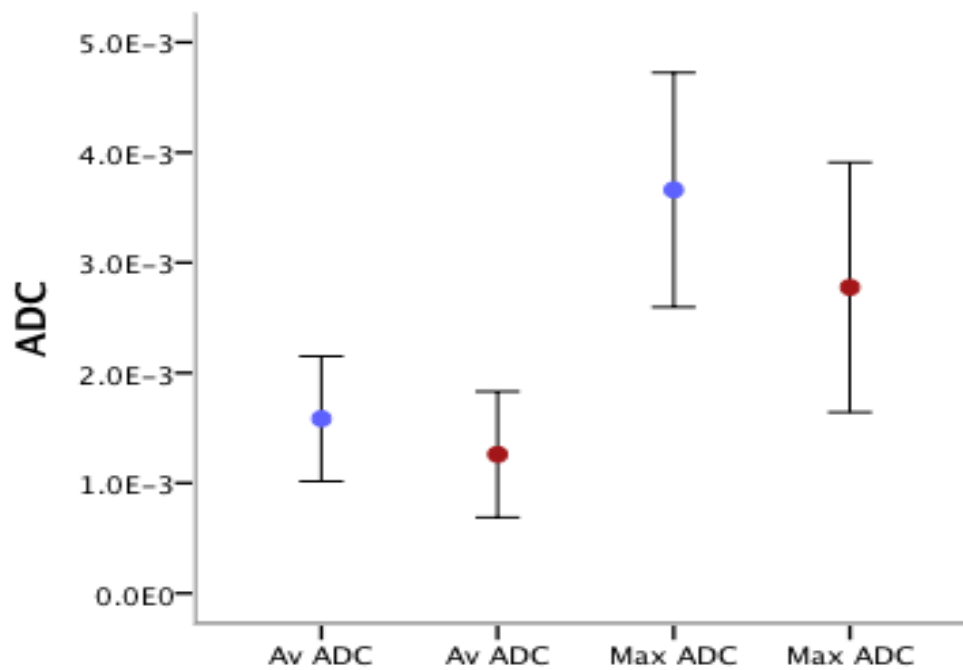


Figure 33: Difference of Av ADC and Max ADC before and after medical therapy.

Pre treatment ● Post treatment ●

3.3.4 DISCUSSION

The art of medical decision making between the gastroenterologists and surgeons in managing acute colitis is to avoid operating in a patient who would eventually have responded to medical therapy and also to avoid undue surgical delay with the associated higher rates of morbidity and mortality due to complications such as peritonitis, sepsis and organ failure. There is no universally accepted simple objective score or marker or modality that can reliably predict prognosis and thereby help in clinical decision making.

In this study different quantitative MRI parameters have been analyzed with regards to their ability to assess disease activity in comparison to a clinical index based on stool frequency and CRP. No significant correlation is found except between fulminant clinical index and contrast enhancement.

As noted in preceding chapters, the use of quantitative measures of contrast enhancement as a marker of inflammation is not clear cut. However this study clearly supports its use and concurs with several other studies in the literature. For example, Low et al (157) used wall thickness and mural enhancement as criteria and found superiority of MRI in comparison to CT for depiction of disease bowel segments even in those with mild disease. Similarly, Koh et al (158) also found bowel wall enhancement (particularly in a layered pattern) to be highly specific for active inflammation in CD. Miao et al (150) described bowel wall thickening, contrast enhancement and mesenteric stranding as the best MRI parameters to determine CD activity and Laghi et al (151) reported high concordance between parietal contrast enhancement and endoscopy and histological scoring of inflammation in children with CD. Maccioni and colleagues (139) also found positive correlation between biological

active disease and bowel wall contrast enhancement together with wall hyperintensity on T2 weighted fat suppressed images

As noted in chapter 1.3, Rimola et al (16, 187) found relative contrast enhancement in addition to wall thickness as the independent predictor of endoscopic disease activity and for presence of ulcers. Conversely other studies have no such relationship between enhancement and activity. Schunk et al (149) found increased contrast enhancement in diseased segments of bowel in comparison to normal segments, but poor correlation with CDAI and CRP. Similarly, Taylor et al (154) found a positive correlation between disease chronicity and contrast enhancement ratio (correlation coefficient 0.82, $p=0.002$) but not with acute or chronic inflammation scores.

Neoangiogenesis is an intrinsic part of chronic inflammation and leads to structural changes including capillary and venule remodeling. This results in expansion of tissue microvascular bed and in increases microvascular permeability.

The effect of increased vascularity on R1 after gadolinium administration is fully explored in the section 3.1, but to summarize an increase in vascular surface area and permeability in inflamed bowel will increase the intra and extra vascular water pool upon which gadolinium can act, thereby increasing relaxivity rate and increasing signal post contrast. In chapter 3.1 I presented data demonstrating inter segmental differences in mural enhancement of normal colon. It would be interesting to “correct” segmental enhancement for these difference to see if the correlation with clinical indices of activity becomes stronger.

One perhaps unexpected finding was the fall in pre contrast R1 after treatment.

Intuitively treatment should reduce mural edema and a rise in relaxivity rate and T1 signal would perhaps be expected. It is possible however the pretreatment R1 was

influenced by mural hemorrhage -clearly bleeding is part and parcel of acute severe colitis. The degree of mural hemorrhage would be expected to decrease with treatment, perhaps explaining the observed drop in R1.

The fall in mural T2 signal after treatment lends weight to the theory that it is a biomarker of inflammation (likely related to mural edema), despite the lack of direct correlation with the FCI. Punwani et al (212) have clearly demonstrated that T2 signal is a strong predictor of inflammatory activity in surgical resection specimens and the apparent robustness of the TCIS (chapter 3.3), which is heavily based on qualitative grading of mural T2 signal, also supports its role. Furthermore I have shown that the score of Steward et al (234), which is based on T2 signal and wall thickness alone correlated with endoscopic CDEIS (chapter 3.2). It is perhaps surprising therefore that the present study found no correlation between T2 signal and the FCI. By way of explanation, FCI is at best a rather imprecise reference standard, although in cases of severe acute colitis where colonoscopy is relatively contra-indicated there are few alternatives. Furthermore there are undoubted problems with quantitative measurements of bowel wall as it is thin and measurements are prone to error. I tried to limit this by using linear (rather than rounded) ROIs to fit the bowel wall contour, but clearly motion and partial volume artifacts will increase ROI errors. My data suggests that qualitative grading of the colon wall signal by radiologists may be more robust than quantitative measures based on ROI placement.

Diffusion weighted imaging makes use of the variability of the “Brownian motion of water molecules” in the tissues which is random. Water molecules are in continuous movement and the rate of this motion or diffusion depends on the kinetic energy of molecules and is temperature dependent. The concept of ADC was introduced to take in account the fact that the diffusion process is complex in biological tissues and can be

affected by many factors such as blood flow in small blood vessels and chemical interaction of water with other macromolecules, which can limit or restrict the amount of diffusion. A low ADC corresponds to high signal intensity/restricted diffusion and high ADC means low signal intensity/more diffusion on these images. Diffusion weighted imaging derives its image contrast from difference in the motion of water molecules between tissue so making ADC directly proportional to the amount of diffusion.

Diffusion weighted imaging has developed a role in neuroimaging (251). Recently its role in assessment of colonic inflammation has been investigated. Kiryu et al (252) reported high accuracy of DWI in evaluation of disease activity as they found lower ADC values in active diseased segments than inactive segments. Oussalah et al (183) DWI hyperintensity as a predictor of colonic endoscopic inflammation with greater accuracy in UC than CD. Oto and colleagues (253) compared DWI with finding of colonoscopy and surgery in patients with CD and found decreased ADC values in inflamed bowel segment reflecting restricted diffusion. In the present study, there was no rise in the value of ADC after treatment and when compared to FCI no significant correlation was found. As mentioned above placement of ROI on bowel wall is prone to error and additional to that it is not easy to visualize minimally inflamed bowel or normal bowel wall on high 'b' value sequences. Furthermore, lack of correlation with FCI is partly due to the fact already discussed that FCI itself is not a sensitive predictor of colonic inflammation.

In conclusion, contrast enhancement seems the most robust quantitative MRI parameters assessing activity of acute colitis in IBD.

4 SECTION FOUR: PATIENT EXPERIENCE AND ACCEPTABILITY OF MRI

4.1 PATIENT EXPERIENCE OF MRCOLONOGRAPHY AND COLONOSCOPY- A QUALITATIVE STUDY

4.1.1 INTRODUCTION

Diagnostic performance is the major determinant for uptake of any radiological investigation but its acceptability to patients is also an important consideration. This is especially relevant in IBD, given the need for repeated colonic examination over the course of disease. Patient acceptance is influenced by several factors, including test expectations, comfort, overall satisfaction and diagnostic performance. Whilst it is assumed that patient acceptance of MRC is higher than colonoscopy, this is based on a limited number of studies as discussed in section 1.3.3.6.

However, existing data has limitations. In particular, it is premature to use quantitative techniques whereby researchers create structured questionnaires based on their own pre-conceived expectations of factors relevant to patients' experiences. Such an approach prevents patients from describing expectations, experiences and preferences in their own words. For example, a recent qualitative investigation of patient experience of colonoscopy and CT colonography (254) revealed important differences in patient experience of staff interactions, previously not considered by the authors, but which had important implications for the associated test anxiety.

Furthermore, the influence of clinical indication has received little attention to date. It is perfectly possible that IBD patients who undergo routine colonic surveillance will have different expectations and priorities than non IBD patients referred for one-off colonic

investigation. Baseline studies with less structured qualitative methods in different patient groups are therefore essential to develop comprehensive quantitative assessments for new diagnostic tests. The aim of this study was to apply qualitative techniques to assimilate data on patient experience and attitudes during MR Colonography and Colonoscopy and to evaluate how this is moderated by clinical indication.

4.1.2 MATERIALS AND METHODS

Between October 2007 and October 2008, 11 male and 7 female patients (median age 40.5; range 17-65 years) were recruited from the MRC study described in chapter 3.2, comparing MRC with same day CC. Patients referred for routine CC were invited to undergo MRC approximately 2 hours beforehand. Of the 18, 10 patients had known colonic IBD, (8 ulcerative colitis and 2 = Crohn's disease, 7 males and 3 females, median age 35 yrs.; range 17-61), and were being assessed during a clinical flare (n=6) or undergoing general surveillance (n=4). Eight patients (4 males & 4 females, median age 48, range 26-65) were undergoing investigation for suspected colonic neoplasia (change in bowel habit n=3, rectal bleeding n=3, and prior history of colonic polyps n=2). All IBD patients experienced at least 1 prior CC compared to just 2 in the non IBD group (for polypectomy). None had undergone prior MRC; although 2 IBD patients had undergone MRI enterography before and 2 non IBD group patients had undergone MRI for other reasons (knee and spine).

All patients underwent full bowel purgation the day before CC. (Appendix C)

4.1.2.1 Patient information

Patients all received the standard colonoscopy information sheet, explaining the procedure including use of sedation and analgesia.

The information sheet pertaining to MRC described the colonic distension with water, need for intravenous Gadolinium injection and the lack of ionizing radiation. The perforation risk from MRC was stated as less than 3 in 10,000 and total duration of test as 30 minutes (Appendix D).

4.1.2.1.1 Procedures

4.1.2.1.1.1 MR Colonography.

The thesis author performed MRC 2 hours before subsequent CC. MRC technique and protocol described in appendix C.

The procedure took between 20 -30 minutes after which the water was allowed to drain back into the enema bag. Patients were then escorted to endoscopy suite.

4.1.2.1.1.2 Colonoscopy

Colonoscopy was performed by experienced operators (2-10 years). Intravenous sedative (Midazolam 50 microgram/ kg, max 10mg and Fentanyl 100 mcg) was administered. Multiple biopsies were taken in those with IBD. Among non IBD patients, 3 had polypectomy and the remaining five had multiple ileocolonic biopsies to exclude microscopic colitis. The procedure took an average of 45 minutes. Patients were provided with refreshments prior to discharge.

4.1.2.1.1.3 Patient Interviews

All patients were interviewed by the thesis author prior to discharge. The interview schedule was constructed in collaboration with a health psychologist (C von Wagner)

with considerable experience of assessing patient experience of diagnostic procedures. Interviews were semi-structured allowing freedom of expression by patients regarding their experience and concerns. Key aspects of each procedure (e.g. anxiety, safety concerns, embarrassment, discomfort, interaction with staff and feedback of results) were identified prior to the interviews in order to allow direct questioning if not mentioned by the patient *do novo*.

Interview transcripts were analyzed using standard thematic analysis (254) which is the most commonly used method of qualitative analysis which involves searching through the data to identify any recurrent patterns. A theme is a cluster of linked categories conveying similar meanings. Analysis was done by the thesis author and Christian Von Wagner, to assimilate individual patient experiences into broad descriptive groups of concerns and interests thus, facilitating overall interpretation of the data. In particular, the data was coded by identifying recurrent themes related to patient perception of their experiences. As codes were accumulated, they were grouped into more general themes by the researchers (thesis author and C von Wagner)

4.1.3 RESULTS

Three main themes emerged from the thematic analysis:

- Physical experience
- Information provision
- Overall preference

4.1.3.1 MR Colonography

4.1.3.1.1 Physical experience

All patients in general expressed mixed views about the physical experience of MRC and several themes emerged.

4.1.3.1.1.1 Water filling

Most patients (both non-IBD, 4/8 and IBD 8/10) described water filling as either uncomfortable or painful and frequently described it as problematic. Filling was mainly associated with episodic cramps, which were mild and tolerable for most e.g. *“For me whole procedure was ok, you do feel little pressure of water filling inside but no pain.”* (IBD patient, male, 29). However, for a sub-group of patients it was intolerable e.g. *“It became quite painful as water was filling in my stomach. It was not pleasant as pain was coming and going. They gave me some injection which made it better for some time but pain came back again and gradually became unbearable.”* (Non-IBD patient, female, 26).

In addition, three patients (2 IBD and 1 non-IBD) expressed anxiety and worry regarding potential incontinence of the water enema. For example *“It was ok except the fluid part, its not a good feeling when water is filling and moving inside, giving the worry that I couldn’t hold it and mess can happen”* (IBD patient, male, 44). Only one patient (non-IBD) actually suffered incontinence suggesting it was the fear of incontinence that was important.

4.1.3.1.1.2 Breath holding

Four patients (three IBD and one non-IBD) found it difficult to hold their breath and/or coordinate with the instructions and timings given *“Sometime breathing was difficult to*

coordinate as there was not much time in between for normal breath”(IBD patient, male, 34). “ Holding the breath was hard specially for such a long time, although near end it became easy, maybe I got use to it” (IBD patient, female, 36).

4.1.3.1.1.3 Lying still in MRI scanner

IBD patients (5/10) in particular described lying in the MRI scanner and restriction of movements as uncomfortable. One patient suggested the use of a TV as distraction *“Lying in same position for an extensive time period and not been able to move is very uncomfortable and in addition there is some weight on your back for the scan, gets unbearable after approximately 20 minutes. There should be something in the room for distraction during scan, something like a TV even without the sound as you have to hear the breathing instruction as well” (IBD patient, male, 61).*

4.1.3.1.2 Information provision

Patients mentioned that they would have preferred instructions about times during examination when they would be able to relax their posture.

4.1.3.1.2.1 Scanner noise

The noise of the scanner interfered with understanding of instructions, particularly amongst non-IBD patients (4/8) who may have been less familiar with diagnostic tests *“The noise and vibration of the MRI machine, was surprising and disrupted communication of instructions” (Non IBD patient, male, 48).*

4.1.3.1.2.2 Information dissemination and uncertainty

Patients expressed mixed opinions about feedback of the test result, although most did comment on the need to wait for the formal MRC report. Non-IBD patients (6/8) however expressed greater anxiety over this delay, *“you don’t get any report, I have to*

wait for my clinic appointment but If you can get report same day it can give some peace of mind” (Non-IBD patient, female, 34).

Another mentioned: *“There was no feedback, I have to wait for the report, but I would like to know as early as possible” (Non-IBD patient, female, 38).*

Conversely, the IBD group (4/10) expressed less anxiety, *“They didn’t give me any feedback; I have to wait for my clinic appointment to discuss with the consultant. I know I have ulcerative colitis so, I am ok to wait to know how I am doing” (IBD patient, male 40).*

4.1.3.1.2.3 Extra colonic findings

Patients of both groups (12/18) were often of the view, that MRI was the more advanced, informative, and safe investigation. It is able to visualize extra-colonic organs, *“There are few things about MRI- it is very advanced technology by which you can see not only one part of tummy but whole of it, which I think is very good to have at one time and there are fewer risk factors, as chance of perforation is very small” (Non-IBD patient, male, 48).*

4.1.3.2 Colonoscopy

4.1.3.2.1 Physical experience

Opinions were mixed but compared to MRC the emerging themes were less varied and concentrated around; air insufflation, colonoscopic manipulation (particularly discomfort below the ribs), and taking of biopsies. As detailed below, despite their familiarity, IBD patients more frequently reported discomfort or pain during CC than non-IBD patients did, particularly during endoscope manipulation.

4.1.3.2.1.1 Pain during colonic insufflation

Patients in both groups (13/18) mentioned discomfort or pain to some degree during air insufflation. *“It was painful continuously not like MR where cramps were episodic, it was severe and all over the tummy. Although it was intolerable they did complete the procedure”* (IBD patient, female, 26).

4.1.3.2.1.2 Colonoscopic manipulation

Both IBD and non-IBD patients associated discomfort/pain with movement of scope particularly amongst the IBD group in which 9 of the 10 patients specifically mentioned painful episodes during the procedure *“It was continuously painful- very bad pain and I think it was happening as they were moving that scope inside”* (IBD patient, female, 17).

Fewer non IBD patients (4/8) also reported pain or discomfort.” *There was discomfort few times during the test. I think it was due to movement of tube, for few minutes and not continuous.”* (Non-IBD patient, female, 38).

Sedation was important moderator of the experience *“I went to sleep during the test but when I woke up at some point I felt some dull pain, only for 5-6 minutes”* (IBD patient, male, 61).

4.1.3.2.2 Information provision

4.1.3.2.2.1 Test Result Feedback

Patients were more satisfied with the feedback they received during and after CC as compared to MRC. They noted the ability to observe the same screen as the physician, whilst, receiving an explanation from the medical team as well either immediately or

later in recovery. *“I was able to see on screen which was fascinating and doctor did explain to me as well that everything was normal”* (Non-IBD patient, female, 40). Some of the patients (both IBD and non-IBD) however, did not find this feedback particularly reassuring, in part due to persistent effects of sedation and lack of full comprehension *“They did explain to me a few things but I can’t remember as I was not very alert due to sedation”* (IBD patient, male, 44).

4.1.3.3 Overall preference

There were divergent views regarding which of the two procedures patients preferred overall and the most important factors influencing their choice.

Of the 18 patients, 10 (56%) stated an overall preference for MRC and 5 (28%) preferred CC. Three patients (17%) did not express any preference, as both tests were very painful and preferred to leave the decision to the clinician. Among IBD group five patients (50%) preferred MRC, three (30%) preferred CC while two (20%) had no preference. On the other hand five non IBD patients (62.5%) had preference for MRC, two (25%) for CC and one patient (12.5%) expressed no preference.

The reasons for preferences were mixed (Table 41). In particular, patients had differing views of which test was more uncomfortable and how this influenced their preference. Duration, safety, perceived diagnostic capability and ability to take biopsies were all noted as specific reasons underpinning stated preferences.

Preference for MRC	Preference for CC
After reading the information and having the both test I think MRI is safer and more informative. (Non IBD patient, male, 65)	Colonoscopy. One reason is being less painful and other I think they can take biopsies, which can be more helpful for the diagnosis and treatment later. (Non IBD patient, female, 48)
MRC was quicker than CC, no sedation was involved so nobody needs to come to take you home. (IBD patient, female, 36)	For me colonoscopy was easier and total time period for the test was shorter as compare to MR. Things during MRI like breathing instructions are difficult to follow specially being on your tummy. (IBD patient, male, 61)
One thing it was more comfortable and I think there are fewer risks with it as it is only water going into your body through a small tube but in colonoscopy tube is very big. (Non-IBD patient, male, 55)	It was more comfortable (Non-IBD patient, female, 36)
It can give more information and it is less invasive. (IBD patient, male, 63)	For me both tests are ok but colonoscopy is more comfortable and you have sedation for it, which you don't have in MRI. (IBD patient, male, 44)
After my experience I would prefer MR. They both are good and MR is more embarrassing but I think it can give more information as compared to colonoscopy.	I would say both are good tests but MR is painful and colonoscopy more comfortable although I think you can get more information through MR but I will

You can take a biopsy during colonoscopy, prefer CC. (IBD patient, 41, male)

which is beneficial but dangerous as it can

damage bowel. (Non-IBD patient, 38

female)

MRI was less invasive just a small tube and

water but in colonoscopy one thing tube is

bigger and then they take biopsy which is

more invasive, there is more manipulation

in it as well. MR (Non-IBD patient, male,

57)

Table 33: Example quotes pertaining to test preference

4.1.4 DISCUSSION

It is clear that patient experience of both MRC and CC is complex and influenced by many factors. The study included patients from two different groups, those with IBD and patients with clinical suspicion of bowel neoplasia (non IBD group).

Most of the prior quantitative studies of MRC and CC experience have included questions on procedural discomfort. Achiam et al (124) used a 5- point pain scale and indicated significantly greater discomfort during CC than MRC, a similar finding to Florie et al (179) who also grouped pain into 5 categories from “none” to “extreme”. In this qualitative study, pain was mentioned more frequently with CC than MRC. All the IBD patients had at least one previous experience of CC but despite this familiarity, they more frequently reported discomfort during CC. The reported beneficial effect of sedation was a common theme and supported by findings from similar samples (181). However, colonic distension with water during MRC was very unpleasant for some,

although the differing degree between individuals was striking, ranging from “a little pressure” to “unbearable”. Using a structured questionnaire in 171 patients, Florie et al (179) also reported that 51% of patients felt colonic filling was the most “burdensome” part of MRC.

I also found that the need to lie still during the MRI is more problematic than previously described, particularly for IBD patients. In addition, the intrusive nature of the MRI scanner noise was noted by several non IBD patients, again a facet of the examination not reported in prior quantitative work.

Although only 1 of the 18 patients suffered any incontinence during MRC but fear of incontinence was stated by several, which is a disadvantage compared to CC.

An interesting outcome of the study is the reported difference in perceived feedback during MRC and colonoscopy. The ability to view the procedure was a distinct advantage of colonoscopy, together with the immediate diagnostic feedback either during the procedure or before discharge. This was particularly noted by the non-IBD group, undergoing investigation for suspected colorectal neoplasia, supporting previous work describing patient’s preference for early feedback, especially in cases of suspected cancer (255). This may explain lower anxiety levels within IBD patients, with known diagnosis and generally not considering a diagnosis of cancer.

An important limitation of the study is that patients were not provided with explicit information on the comparative diagnostic accuracy of MRC and CC. Previously in comparison of CT Colonography and CC, relative diagnostic performance had a major influence on overall patient preference (256). However, I was still able to elicit

interesting perceptions from patients about the diagnostic capabilities of MRI such as a “new”, “expensive” and “superior” technology as compared to CC.

Patients perceived the ability of MRI to visualize beyond the colon as a definite advantage, along with its superior safety profile. This supports the findings of prior CT colonography research (254) that patients are intrigued by the ability of modern scanners to image organs outside the large bowel. However, patients are often unaware that this may sometimes trigger subsequent tests to investigate unexpected findings. There are of course strong parallels between CT colonography and MRC in this respect.

Although there was a slight overall preference for MRC, this tendency was not strong. Furthermore, a large range of factors influenced patients’ preferences with marked inter-individual differences. Simply asking patients “preference” in quantitative studies is overly simplistic giving the complexity of underlying determinants of patient opinion.

This study had built on the existing literature regarding comparative patient experience during MRC and CC. By using qualitative methods I have identified new aspects of MRC, which directly impact on patient preference including the need to lay still, noise from the scanner, fear of incontinence, delayed diagnostic feedback and perceived diagnostic performance of the “new technology”. Although the study included a small sample size, this is the norm for a qualitative study like this and useful information has been gleaned. However further study using a larger sample size may well be worthwhile given the wide range of patient opinions found. I also acknowledge that MRC is a developing technique with a multitude of approaches advocated for bowel preparation (full or reduced), colonic insufflation (liquid or gas) and MR sequence selection. This

data may not therefore be directly applicable to institutions using differing MRC protocols.

I did find clear differences in the importance of these factors to patients with differing clinical indications. Such data has important implications with regards to the provision of patient information for those undergoing MRC. Focus should be placed upon increasing the detail and relevance of information media. It can also assist the design of future quantitative measures of patient experience, by incorporating the additional dimensions and considering clinical indications to allow sub-group analysis. These findings should also be followed up by more direct ways of testing patient preferences using strategies such as conjoint analysis and discrete choice modeling, a procedure used frequently for health economic research. Data gathered in the study would be instrumental when asking people to balance risks and benefits associated with invasive and non-invasive testing modalities.

In conclusion, patient experiences of MRC are complex. The assumption MRC is better tolerated and preferred to CC is not valid for all patients. Individuals place differing personal weightings on the relative importance of test attributes, which defines overall test preference. Informed discussion prior to requesting specific colonic investigations would likely improve current clinical practice.

4.2 ASSESSMENT OF PATIENT ACCEPTANCE OF MRCOLONOGRAPHY VS COLONOSCOPY

4.2.1 INTRODUCTION

In the previous chapter, I used interviews and qualitative techniques to identify which aspects of MRC and endoscopy were least acceptable to patients, and which factors influenced preference.

My findings were that patient experience of investigations is complex and in part dependent on previous experience of investigation and the target lesion (i.e. potential of malignancy or known benign IBD). The potentially shortcoming of researcher-designed questionnaires were also highlighted-important facets of patient experience are often excluded by questionnaire devised by medical staff. Nevertheless, patient experiences of colonoscopy have received considerable attention in the past.

Questionnaires have been developed based on the process of principal component analysis following patient interview (as I did in the previous chapter for MRC). One such questionnaire is widely used in assessing experience of endoscopy has been devised by Salmon et al (244, 257). Indeed this questionnaire has also been applied to radiological tests of the colon, including barium enema and CT colonography (244, 257, 258). As previously discussed in session 1.2.3, colonoscopy is the gold standard for diagnosis and disease assessment in IBD and other colonic pathologies but the procedure can have limited patient acceptance due to the need of bowel preparation, pain and embarrassment. If MRC is to be a viable alternative to colonoscopy, comparative patient acceptance must be at least as good as for colonoscopy, and ideally better due to its intrinsic limitations (e.g. inability to obtain biopsy tissue). In this chapter I formally

evaluate patient experience of MRColonography (MRC) in comparison to conventional Colonoscopy (CC) using the validated questionnaire devised by Salmon et al (244).

4.2.2 MATERIALS AND METHODS

Thirty one patients were recruited from the studies investigating the utility of MRC described in chapter 3.1 and 3.2. All patients underwent MRC prior to same day colonoscopy as described fully in these chapters.

Among these nineteen patients were referred for colonoscopy for either confirmation of new clinical diagnosis of IBD or surveillance. Eight patients needed colonoscopy due to change in bowel habit and the remaining three patients had CC as part of polyp surveillance. 16 patients (13 IBD and 3 non IBD) had previous experience of CC but none of them had MRC before (Table 34).

	IBD	Non-IBD
No of patients	19	12
Age (mean, range)	25.5 (17-64)	42.33 (25-64)
Females (mean age and range)	9 (34.33, 17-50 yrs.)	6 (34.83, 25-47 yrs.)
Males (mean age and range)	10 (42.7, 30-64 yrs.)	6 (49.83, 40-64 yrs.)

Table 34: Patient demographics

A validated satisfaction questionnaire with 25 items (marked from 1 to 7) presented together with their opposite was administered after both tests (Appendix E). A higher

score reflects more positive response. These responses were grouped into 3 principal components (physical experience, worry and satisfaction) by the authors of the questionnaire. All the patients completed both the proformas before leaving the hospital and collected by thesis author. Overall patient preference was canvassed 2 weeks later (Appendix F). All patients were given the proforma to take home and were asked to post it after filling in stamped addressed envelope. In particular, the follow up questionnaire asked patients to grade the tolerance of both procedures

Well/ fairly well/poorly/ very poorly

They also selected the worst part of the procedure, noted the recovery time and listed any reasons for a longer time of recovery. Patients were also asked to express which investigation they found more acceptable and which they would prefer in future and if they would be willing to have each procedure again.

4.2.2.1 Statistical Analysis

Initial analysis of the seven-point questionnaire indicated that responses were skewed toward the upper end of the distribution so nonparametric methods were applied. Data regarding patient responses about MRC and CC was compared using Wilcoxon matched pairs and one-sample test of portions for follow up questionnaire.

4.2.3 RESULTS

All the patients filled the questionnaire before leaving the hospital and patient experience was grouped into three components

1. Physical experience
2. Patient worry
3. Patient satisfaction

4.2.3.1 Physical experience

Patients found CC overall physically less comfortable than MRC (Median 32 vs. 41, $p=0.031$). For example, they reported they were more weary after CC (median 2 vs. 3 $p=0.05$) had more soreness during the procedure (median 3 vs. 4 $p=0.021$), and preferred to be less awake during CC (1 vs. 3, $p=0.007$). They did however feel in better control during CC than MRC (median 6 vs. 7 $p=0.053$) (table 35, figure 34).

Variable	MRC Median (IQ)	CC Median (IQ)	Value of p
Weary	3 (2,7)	2 (1,6)	0.05
Pain	4(3,7)	3(2,7)	0.276
Comfort	2(1,5)	2(1,3)	0.24
Experience	4(3,7)	4(3,6)	0.107
Control	7 (3,7)	6(3,7)	0.05
Soreness	4 (2,7)	3 (2,7)	0.021
Fool of self	7 (4,7)	7 (6,7)	0.211
Relieved when over	2 (1,4)	2 (1,3)	0.481
Preferred to be more awake	3 (1,4)	1(1,3)	0.007
Sum	41(24,51)	32 (21,41)	0.031

Table 35: Comparison of Patient's physical experience during MRC and CC

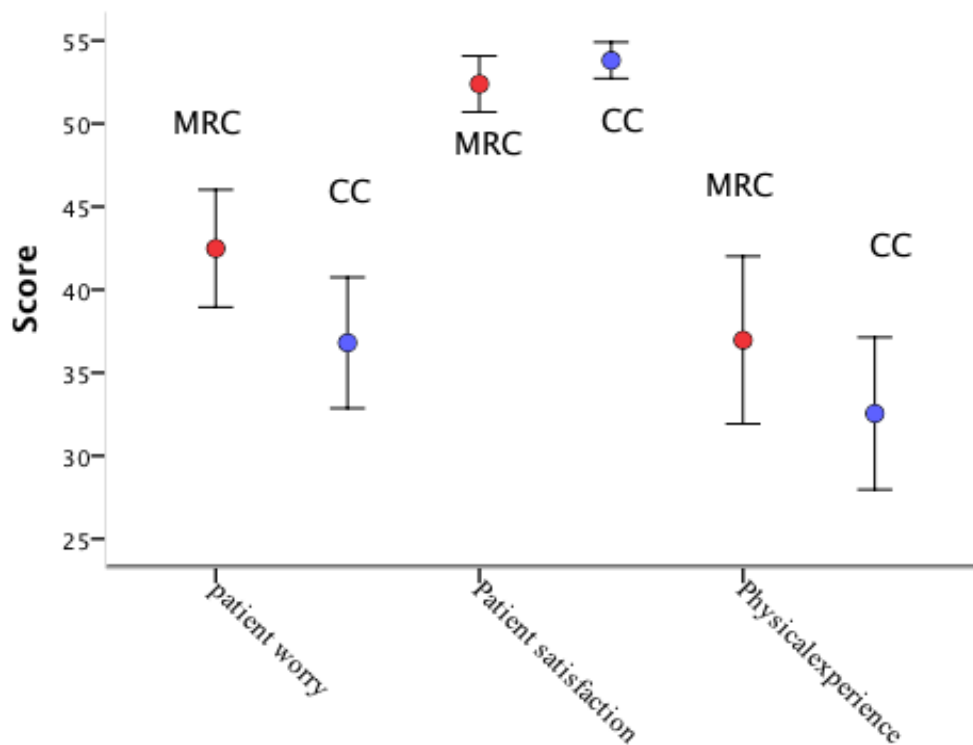


Figure 34: Comparison of MRC and CC split according to the three main components

4.2.3.2 Patient Worry

Patients were considerably more worried during CC than MRC (2 vs. 6 $p < 0.001$) and they were more concerned what would be found during CC than MRC (2 vs. 4 $p = 0.01$). However they did find MRC as not what they had expected compared to CC (3 vs. 1 $p = 0.01$). Overall patients were significantly more worried about CC than MRC (38 vs. 46 $p < 0.001$) (Table 36, figure 35).

Variable	MRC	CC	Value of p
	Median	Median	
	(IQ)	(IQ)	
Frightened	7 (4,7)	7 (2,7)	0.084
Worried	6 (3,7)	2 (2,6)	<0.001
Agitated	7 (4,7)	7 (3,7)	0.22
Worried what to find	4 (2,6)	2 (2,6)	0.01
As expected	3 (1,6)	1 (1,3)	0.01
Understood	7 (4,7)	7 (5,7)	0.333
Puzzled	7 (6,7)	7 (4,7)	0.221
Confused	7 (6,7)	7 (5,7)	0.099
Sum	46(37,50)	38 (29,47)	<0.001

Table 36: Comparison of patient worry about MRC and CC

4.2.3.3 Patient satisfaction

There was no significant difference in overall patient satisfaction after both procedures ($p=0.17$). They were equally satisfied about the staff interaction and information provision. They also expressed same level of confidence in staff for both the procedures and they felt equally dignified during both procedures as well (Table 37, figure 35).

Variable	MRC	CC	Value of p
	Median	Median	
	(IQ)	(IQ)	
Satisfied	7 (6,7)	7 (6,7)	0.068
Staff interested	7 (7,7)	7 (7,7)	0.178
Pleased	7 (6,7)	7 (7,7)	0.141
Staff warm	7 (7,7)	7 (7,7)	0.109
Staff informative	7 (7,7)	7 (7,7)	0.028
Dignified	7 (5,7)	7 (5,7)	1
Interested	7 (7,7)	7 (7,7)	0.5
Confidence	7 (7,7)	7 (7,7)	0.109
Sum	53 (50,56)	55 (55,56)	0.177

Table 37: Comparison of patient satisfaction after MRC and CC

4.2.3.4 Follow up Questionnaire

Out of 31 total patients, the majority patients tolerated MRC well (17, 54.8%) or fairly well (7,22.6%) whereas 21(67.7%) tolerated CC well and 5 (16.1%) tolerated it fairly well (Figure 36).

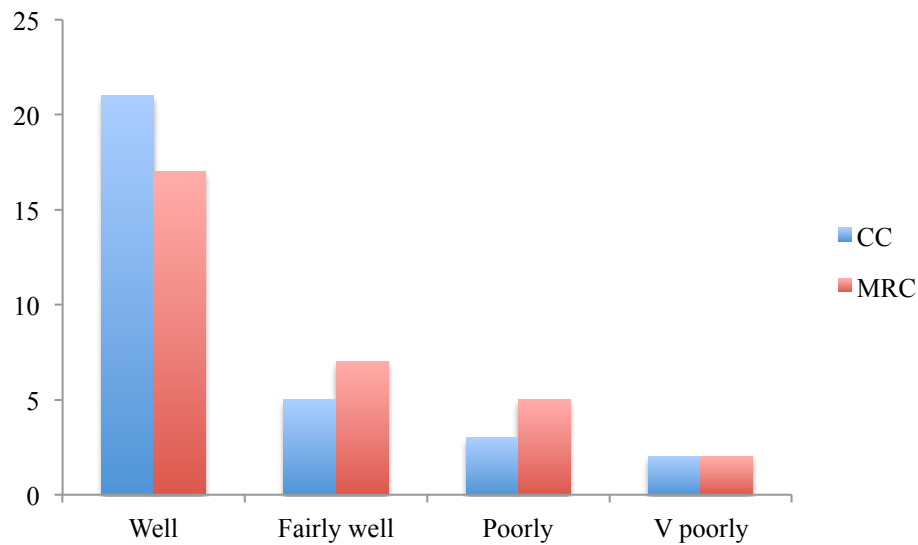


Figure 36: Bar graph – patient tolerance for MRC and CC

Regarding recovery time after MRC, the majority of patients recovered in less than one hour after the scan (18, 58.1%, $p = 0.002$). In comparison 12 (38.7%) patients took between 1-3 hours and 11 (35.5%) took more than 6 hours to recover after CC (Figure 37 and 38).

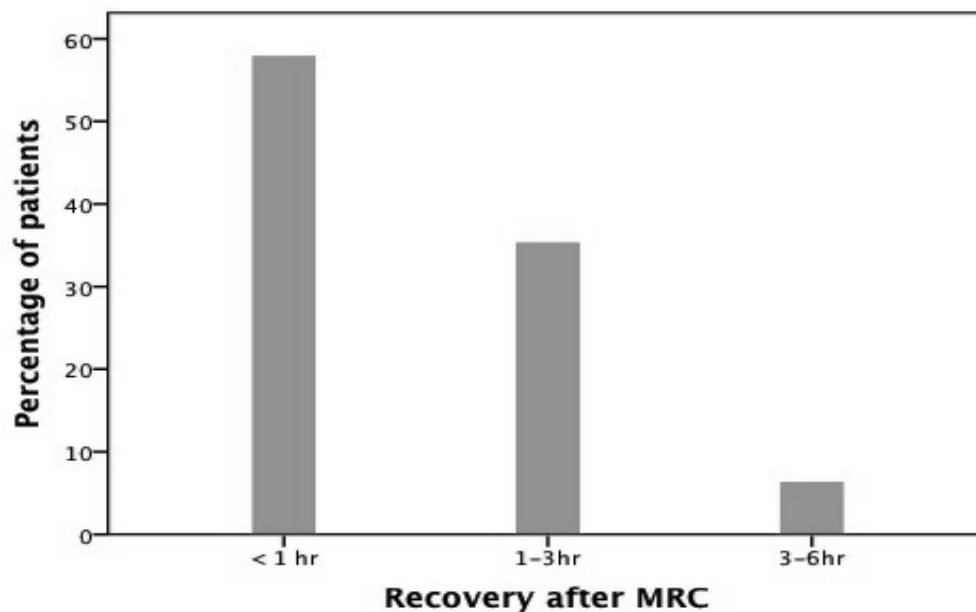


Figure 37: Bar graph representing patient recovery after MRC

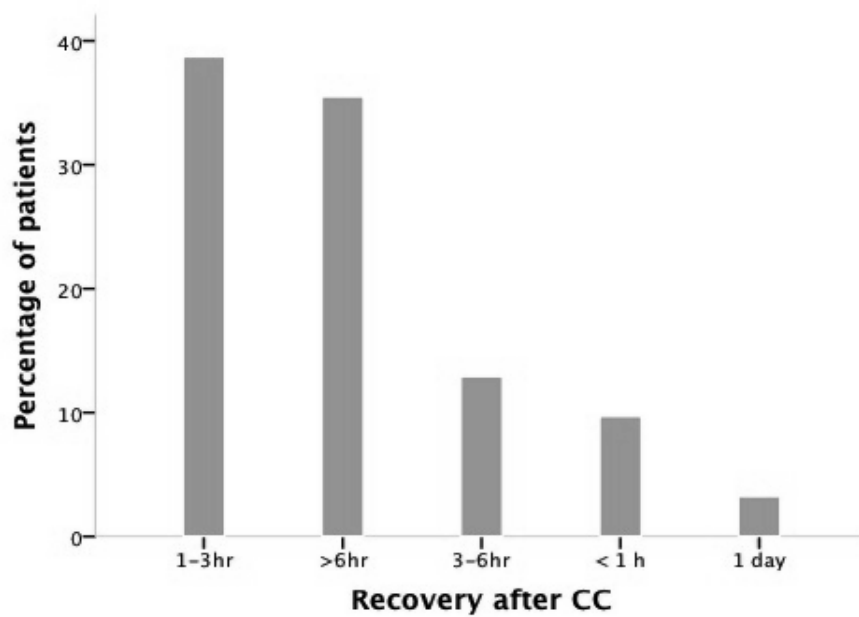


Figure 38: Bar graph representing patient recovery after CC

On inquiring about the worst part of these investigations, 23 (74.2%) patients found insufflation with water during MRC as the worst part while 14 (45.2%) patients found maneuvering of the colonoscope as the worst part of the procedure (figure 39 & 40).

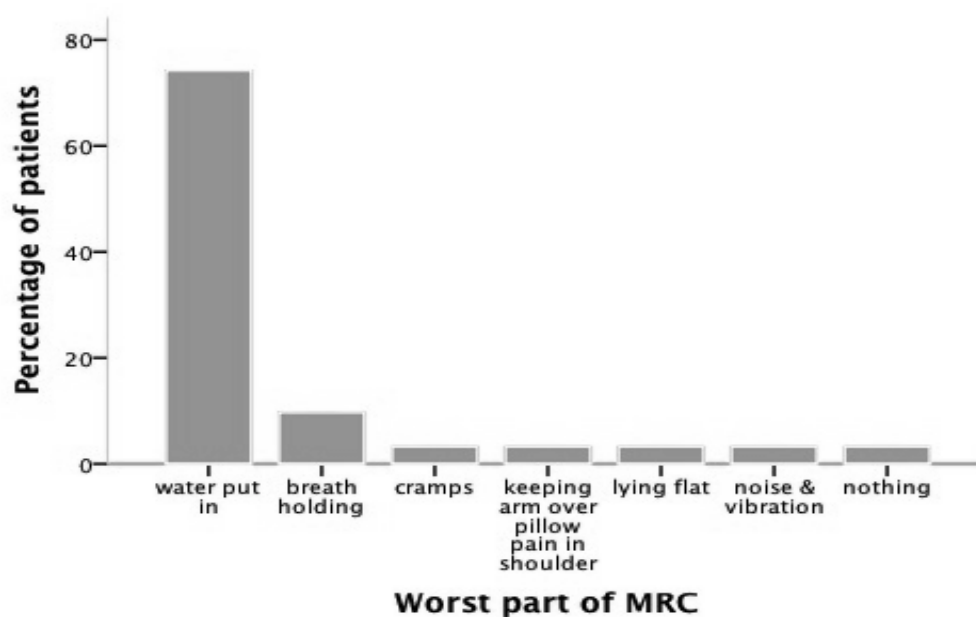


Figure 39: Bar graph representing worst part of MRC

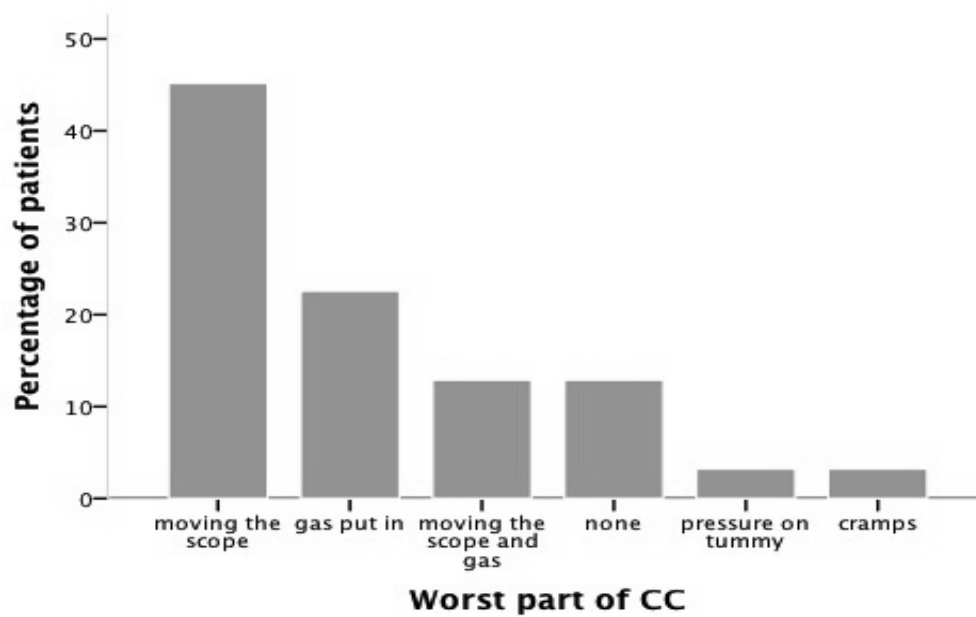


Figure 40: Bar graph representing worst part of CC

When patients asked about having either investigation again, 27 (87.1%) would have MRC again if required and 24 (77.4%) would have CC ($p=0.3$). For the majority of patients MRI was the most acceptable test (16, 51.6%) 11 patients (35.5%) viewed MRC and CC as equally acceptable and only 4 (12.9%) found CC as the most acceptable investigation ($p=0.001$) (figure 41).

In terms of overall preference 14 (45.2%) patients selected MRC as the preferred investigation in comparison to (6, 19.4%) for CC whereas, 11 (35.5%) patient had no preference (Figure 42).

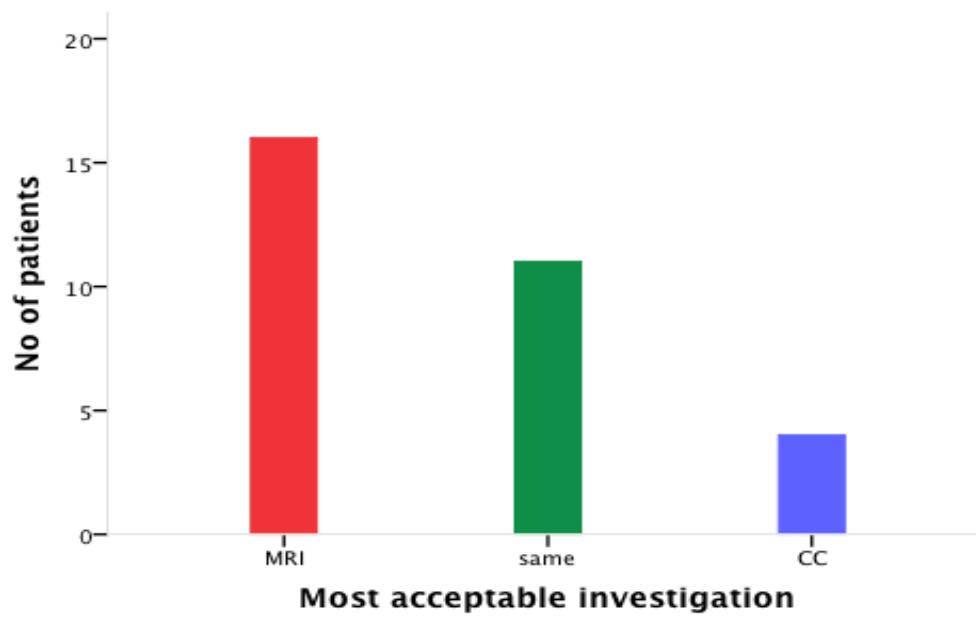


Figure 41: Bar graph representing patient's selection of the most acceptable investigation

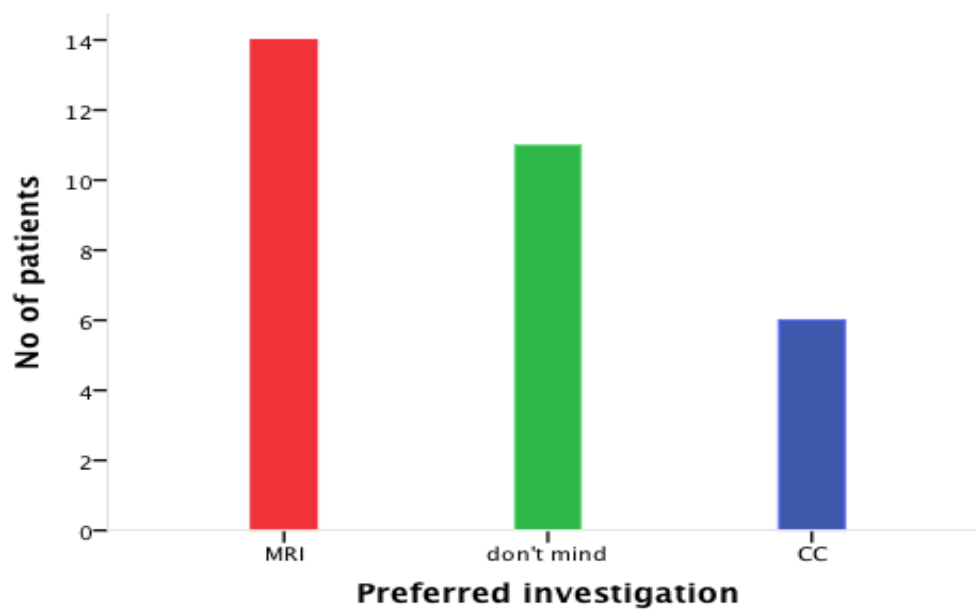


Figure 42: Bar graph representing patients' preference regarding future investigation.

4.2.4 DISCUSSION

Different methods have been proposed for colonic examination with varying sensitivities and specificities. Colonoscopy stands as the gold standard at present both for IBD and non IBD patients. Despite its high sensitivity and specificity, the examination is invasive, with potentially serious complications. Furthermore, procedure related patient discomfort such as that caused by scope movement influences patient satisfaction and acceptance of test.

Patient acceptance is influenced by several factors, notably anticipation about the investigation and previous experience. This has led to the assumption that patient acceptance would be higher with non-invasive examinations as compared to more invasive ones.

Florie et al (179) used a five - point scale to assess physical experience of MRC (limited bowel cleansing) and CC (full bowel cleansing) and a seven - point scale to evaluate patient preference. Participants found MRC less burdensome and less painful ($p < 0.001$). They also found higher patient preference for MRC immediately following ($P < 0.001$, 69% vs. 22%) as also five weeks after the investigation ($p < 0.001$, 65% vs. 26%).

Kinner et al (259) compared patient' acceptance between MRC and optical colonoscopy (OC). The overall rating of OC and MRC was not significantly different, 46% of patients preferred MRC whilst 44% preferred OC.

Achiam et al first in 2007 (124) and later in 2010 (180) compared MRC (with fecal tagging) with CC. In first study patients reported a preference for MRC for future investigation (66 % vs. 10%) and in second study they found same trend with 71% of patient preferring MRC to CC. When asked patient reported preference for MRC even if

done with bowel purgation (75% vs. 12%) as they found MRC less painful and less unpleasant.

Hartman and colleagues (173) also compared patient acceptance of MRC and CC and reported higher preference for MRC over CC (58% vs. 20.5% of patients).

In the present study, patients found CC less comfortable and more painful than MRC. They also were more worried by the procedure. Patients in particular identified movement of scope and insufflation of gas as being the worst parts of CC. Similarly they noted insufflation of water during MRC as uncomfortable but overall MRC was reported to be less painful than CC. This data concurs with the literature – that CC in general is more uncomfortable than MRC despite use of sedation in the former. This also concurs with my qualitative interview study in chapter 4.1.

Patients also expressed more worry about CC and concern about what could be found. Despite these differences between CC and MRC, patients were equally satisfied with the two tests. Notably they were equally pleased after the two tests, find staff generally warm and helpful and felt both procedure were dignified.

The follow up questionnaire elicited patient's views on overall test acceptability and preference. Akin to chapter 4.1, patients held mixed views with some preferring CC, some MRC and several having no preference. However in general patients tended to find MRC more acceptable than CC and preferred it over endoscopy. This again concurs with many of the previous questionnaire studies published in the literature as described above. However as I have presented in chapter 4.1, patient preference is much more complex than simply ticking one test over another. The drivers of preference cannot be elicited by standard questionnaires. Test safety, diagnostic accuracy, ability to see outside the colon etc. were all stated as drivers of patient preference during face to

face interviews as described in chapter 4.1 and it seems likely these were also considered as important by patients when they completed questionnaires. However the physical experience of the tests presumably also played an important part given patients reported more physical discomfort and worry during CC.

Of course the study design has limitations. The patient experience and expectations of colonoscopy and MRI are highly dependent on the patient information given. Patients were given information sheets pertaining to colonoscopy and MRI and the risk of perforation mentioned in both. However it is possible difference in the information relayed to patients on these different sheets could influence their expectations and preferences. We also of course relied on patient assessment of the outcomes rather than using an independent reviewer. For example it is possible that if the MRI had missed important disease seen at colonoscopy this would have significantly affected the patient preference for the test had this information been given. As it was, this study assessed patient perceptions of the tests including their perceived advantages and disadvantages. Finally because of the study design MRI always preceded colonoscopy, which could have influenced patient experience. For example patients could have been tired following the MRI, which could adversely influence their experience of the colonoscopy.

In summary, patients found MRC more comfortable and less painful than CC and they recovered quicker after the procedure. Although patient satisfaction and preference for diagnostic tests is complex but above features have translated into overall patient preference and acceptance of MRC. This suggest that from the point of view of patients, MRC is an acceptable and for some preferable alternative to CC.

5 CONCLUSION

5.1 Introduction

This thesis has examined the use of MRI in enteric inflammatory bowel disease including its level of dissemination in the NHS and its impact on the diagnostic confidence of clinicians and therapeutic strategy. The role of unprepared MRI in evaluation of acute colitis using both qualitative scores and quantitative parameters is assessed. An attempt is made to define post contrast perfusion kinetics of normal colon during MRC and to evaluate the utility of MRC to assess colonic disease activity against endoscopic and histological reference standards. Finally patient experience of MRC and CC is investigated with help of qualitative interviews and quantitative questionnaires.

5.2 Discussion of Results

Whilst European guidelines increasingly advocate the use of cross sectional techniques (particularly MRI and SbUS), barium studies remain the imaging investigation most commonly performed in both diagnosis and assessment of CD in all age groups in UK. Although the majority of UK radiology departments now have access to MRI, in my national survey only 38% offered small bowel MRI, and then mainly for patients with known CD or with a high clinical suspicion. Radiologists were more likely to use MRI than gastroenterologists request it. MR Enterography is more widely used than MR Enteroclysis despite the potential higher sensitivity of the latter (190). The level of dissemination of SbUS is also limited in UK as only 46% of departments perform it. CT is currently preferred mainly for detection of extraluminal complications. There is a

trend of using MRI and SbUS more frequently in younger patients instead of using tests, which impart ionizing radiation. I can thus conclude that at the time of my survey, a sizable minority was using MRI in clinical practice within the NHS. Possible barriers to implementation include lack of randomized trial data demonstrating its superiority over conventional tests, lack of MRI access and capacity, perceived expense and lack of experience amongst radiologists and requesting gastroenterologists. Given international committee recommendations that MRI should be used as a first line test in IBD it is likely UK departments must overcome these barriers as the technique disseminates.

MRE is intuitively a very attractive proposition for management of CD but there is no robust reference standard to assess its diagnostic efficacy. A framework for assessing effectiveness of radiological investigations was proposed by Fryback and from this various methodologies have developed including the effect of tests on diagnostic decision making and treatment strategy. In an attempt to assess the therapeutic and diagnostic impact of MRE in CD I administered a detailed proforma to requesting clinicians. I found that a negative MRE report is highly effective in reassuring clinicians about the absence of small bowel disease. . Furthermore, changes in diagnostic confidence influences therapeutic strategy in around 50% of patients with suspected disease, in 77% of patients with a strong clinical suspicion and overall in 61% of patients.

From this study, I can conclude that when used as part of an established service, MRE has a positive effect on clinician diagnostic confidence, which translates into real changes in therapeutic management in the majority of patients. This data should provide supporting evidence for those wishes to introduce MRE into their practice.

MRColonography has been advocated as a potential safe and accurate diagnostic tool to accurately document the location, extent and severity of colonic inflammation. Various parameters have been reported to correlate with disease activity during MRColonography, particularly wall thickness, T2 signal and contrast enhancement. The literature is mixed regarding post gadolinium enhancement and one of the possible explanations for this is intersegmental difference in normal colon due to differing blood supplies. In an attempt to evaluate this potential difference, dark lumen MRC was performed in patients who had normal or non inflamed colon on endoscopy. No significant difference was seen in pre contrast R1 values between ascending colon (AC), descending colon (DC) and rectum but $\Delta R1$ (change after contrast) was greater for the ascending than descending colon. AUC-R1 of the AC was also significantly greater than the DC and there also were differences between rectum and other colonic segments. The data may be explained by known anatomical differences in blood supply between the right and left colon. From this data I can conclude that segmental differences in colonic enhancement should be considered when using enhancement as biomarker for colonic inflammation.

Three proposed qualitative MRI scores of IBD activity were then tested using dark lumen MRC against an endoscopic (CDEIS) and histological standard of reference. All three tested scores (Steward score, MRI activity index and MaRIA index) correlated significantly with CDEIS on per patient and per segment basis. Wall thickness and T2 signal were common parameters in all these scores, with contrast enhancement also considered in calculating the MRI activity score and MaRIA score. The strength of correlation with CDEIS was not overtly less with the simple Steward score (based on just wall thickness and T2 signal) in comparison to the other two more complex scores, suggesting contrast enhancement may not add to accuracy when scores are based on

subjective assessments by radiologists. From this study I can conclude that enteric and extra-enteric parameters provided during MRC can be subjectively graded by reporting radiologists and act as robust biomarkers of disease activity. MRC may therefore have a role in not only staging disease, but also for therapeutic monitoring

In patients with acute colitis, invasive tests just as endoscopy or full MRC are usually inappropriate. Unprepared MRI was tested as a rapid non invasive alternative of assessing disease severity. A Total colonic inflammatory score (TCIS) based on haustral loss, Mural T2 signals, wall thickness, pericolonic mesenteric edema, small bowel and colonic dilatation was derived, and correlated with clinical markers of disease severity. A significant correlation was seen between pre treatment TCIS and both CRP and stool frequency. Furthermore, there was significant reduction in TCIS, CRP and stool frequency after medical therapy. No correlation was found between TCIS, CRP and stool frequency after medical therapy. Interestingly admission TCIS showed a significant correlation with length of inpatient stay, suggesting it may have a potential role as new prognostic tool. In this regard it was superior to conventional AXR. Overall the MRI was reasonably acceptable to patients.

From this study I can conclude that unprepared MRI is a valid alternative to conventional clinical markers of disease activity in acute severe colitis, providing information about the extent and severity of disease. The short 10 min protocol is tolerated by patients and clearly safer than invasive endoscopy. The use of unprepared MRI in assessing acute colitis is justified.

In a further attempt to quantify disease severity in acute colitis quantitative, measurements via RIO placement was undertaken using dynamic contrast enhanced T1 weighted images, diffusion weighted images and T2 weighted data before and after medical treatment. Data were correlated with Fulminant colitis index (a clinical

standard of reference based on CRP and stool frequency). No significant correlation was found between FCI and most parameters other than with contrast enhancement, where a positive correlation was confirmed. However, there was a significant fall in mural T2 signal after treatment. Quantitative measurements of thin bowel wall are prone to error and motion and volume artifacts can increase these errors. In addition, FCI is an imprecise reference standard compared to colonoscopy but later is relatively contra indicated in acute colitis. The data in patients with acute colitis suggests that qualitative grading may be more robust than quantitative measurements based on ROI placement.

Patient experience is complex and influenced by many factors. I investigated this by direct face to face patient interviews, and by use of a questionnaire validated for colonoscopy. From the interview data I found that patients with IBD find the need to lie still difficult where as those without IBD in particular found the scanner noise intrusive. Some patients find the fear of incontinence during MRC as a disadvantage. The ability to view the procedure and immediate feedback during CC was seen distinct advantage especially amongst those without IBD. Conversely, patients perceived the ability of MRC to visualize beyond the colon as a definite advantage. Based on the questionnaire responses, it seems patients find MRC more comfortable and less painful than CC and they recovered quicker after it. I did find an overall slight preference for MRC in terms of perceived patient acceptability and preference, although many graded both tests as equal. It is clear however that patient experience is governed by many facets over and above the physical experience of the test.

5.3 Conclusion

IBD is a lifelong condition that remains a diagnostic and therapeutic challenge and requires repeated assessment of disease extent and activity as part of management.

The use of MRI for IBD has dramatically risen in recent years but in UK there is only moderate dissemination of MRI and SbUS as barium follow through remains the most frequently performed and requested examination for known or suspected luminal small bowel CD. However, MRE has a positive diagnostic impact in patients under investigation for small bowel CD and significantly influences in therapeutic strategy of these patients.

There are inter segmental differences in colonic enhancement should be considered when using enhancement as a biomarker for colonic inflammation. Qualitative parameters particularly, wall thickness and T2 signal assessed during dark lumen MRC correlate well with endoscopic disease activity (CDEIS), suggesting MRC a complementary tool to CC in the follow up of patients with colitis.

A MRI parameter scores (TCIS) derived from unprepared T2 weighted images in acute severe colitis performed well compared to conventional clinical markers of severity, and may act as a prognostic marker. Quantitative region of interest based measurements fared less well, although contrast enhancement was correlated with a fulminant colitis index. My data suggests that qualitative grading of colon wall is more robust than quantitative measures.

Patient experience during MRC is part dependent on the reason for colonic investigation (be it IBD or non IBD). Patients do find the some of the physical experiences during MRC as unpleasant (for example lying still, scanner noise, water instillation and fear of incontinence). However in general, they found MRC less uncomfortable than colonoscopy. Overall patient preference was mixed but there was a slight bias in favour of MRC.

In summary, this thesis has shown MRI is a robust diagnostic technique, which has a valid clinical role in assessment of small bowel and large bowel in IBD. It can compliment endoscopy and other radiological modalities and can act as biomarker of disease activity.

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APPENDIX

Appendix A- Gastroenterologist Questionnaire

1. In a patient with newly diagnosed, biopsy proven, Crohn's disease which test(s) would you normally request to assess small bowel involvement in the following age groups? (You may tick more than one test if multiple concurrent tests are normally requested.)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

2. In a new patient with a high clinical suspicion of small bowel Crohn's disease e.g. chronic diarrhea, abdominal pain and weight loss with anaemia, thrombocytosis and a raised CRP etc. which test would you normally request to establish a diagnosis of Crohn's disease? (You may tick more than one test if multiple concurrent tests are normally requested.)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Colonoscopy with ileoscopy and biopsies				

Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

3. In a new patient with a low clinical suspicion of small bowel Crohn's disease e.g. with occasional diarrhoea, vague abdominal pain and no weight loss or anaemia, and a normal CRP which test would you normally request to exclude small bowel Crohn's disease? (You may tick more than one test if multiple concurrent tests are normally requested.)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Colonoscopy with ileoscopy and biopsies				
Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

4. In a patient with known small bowel Crohn's disease in whom an extraluminal complication such as fistula or abscess is suspected which of the following tests would you routinely request?

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

5. In an out-patient with known Crohn's disease and symptoms suggestive of stricturing disease which of the following tests would you routinely request to determine the level of obstruction? (You may tick more than one test if multiple concurrent tests are routinely requested)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

1. In a patient with known Crohn's disease with a clinical flare-up of the disease which test would you routinely request to reassess the small bowel? (You may mark more than one test if multiple concurrent tests are routinely requested)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through/Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI				
CT +/- CT Enteroclysis				
Capsule Endoscopy				

Appendix B- Radiologist Questionnaire

1. In your department in a month, on average, how many of the following investigations do you perform for diagnosis or follow up of small **bowel Crohn's disease**? (Please put numbers in the appropriate box, if none are performed please place a 0 in the appropriate box)

Investigation	Number performed for suspected diagnosis	Number performed for follow up of disease
Barium Follow Through		
Barium Enteroclysis		
Small Bowel Ultrasound		
Small bowel MRI (oral contrast)		
MRI Enteroclysis		
CT (oral contrast)		
CT Enteroclysis		
Capsule Endoscopy		

If you perform small bowel MR please state

Your preferred oral contrast agent if any? _____

2. In a patient with **biopsy proven newly diagnosed Crohn's disease** which investigation would you normally use, if any, to assess small bowel involvement in the following age groups? (You may tick more than one investigation per age group if multiple concurrent investigations are usually performed.)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow				

Through				
Barium Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
Small bowel MRI (oral contrast)				
CT (oral contrast)				
CT Enteroclysis				
Capsule Endoscopy				

3. In a patient with **clinical suspicion of small bowel Crohn's disease** but **no biopsy proof**, which of the following investigations would you normally use for diagnosis in, in a patient with a) high clinical suspicion of disease and b) low clinical suspicion of disease? (You may tick more than one investigation per age group if multiple concurrent investigations are normally performed.)

a) In a patient with **high clinical suspicion** of disease?

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through				
Barium Enteroclysis				

Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
MRI Enteroclysis				
CT (oral contrast)				
CT Enteroclysis				
Capsule Endoscopy				

b) In a patient with **low clinical suspicion** of disease?

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through				
Barium Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
MRI Enteroclysis				
CT (oral contrast)				
CT Enteroclysis				

Capsule Endoscopy				
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4. In a patient with **known Crohn's disease** in whom an **extraluminal complication** such as fistula or abscess is clinically suspected which of the following investigations perform to confirm this?

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through				
Barium Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
MRI Enteroclysis				
CT (oral contrast)				
CT Enteroclysis				
Capsule Endoscopy				

5. In an **out-patient with known Crohn's disease** and **obstructive symptoms** suggesting stricturing disease which of the following tests would you normally perform to determine the level of obstruction? (You may tick more than one investigation if multiple concurrent investigations are normally performed)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through				
Barium Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
MRI Enteroclysis				
CT (oral contrast)				
CT Enteroclysis				
Capsule Endoscopy				

2. In a patient with **known Crohn's disease** with a **clinical flare-up** which test would you normally perform to reassess the small bowel disease? (You may tick more than one investigation if multiple concurrent investigations are normally performed)

Investigation	Patient <20 years old	Patient 21 – 40 years old	Patient 41 – 60 years old	Patient >61 years old
Barium Follow Through				
Barium Enteroclysis				
Small Bowel Ultrasound				
Small bowel MRI (oral contrast)				
MRI Enteroclysis				
CT (oral contrast)				
CT Enteroclysis				
Capsule Endoscopy				

Appendix C- MR Colonography

Patient preparation

- All patients underwent solid food restriction from lunchtime the day before colonoscopy followed by full bowel purgation- 10 Senna tablets and two sachets of magnesium citrate (Citramag- Sanochemia Diagnostics, UK) dissolved in one litre of water.
- Rehana Hafeez performed MRC 2 hours before colonoscopy in all patients.
- Following rectal introduction of 16F Foley catheter, the colon was gently filled with 1.5l of warm tap water from an enema bag held at shoulder height (i.e. filling by gravity).
- Bowel motility was abolished by intravenous spasmolytic (Buscopan, Boehringer Ingelheim, Germany) 0.3mg/kg (maximum 20 mg) immediately prior to abdominal imaging
- Once the colon is distended, a standard MR scanning protocol was performed in all patients and the procedure took an average 30 minutes.

MRC protocol

Images were acquired in the prone position with a 1.5T Siemens Avanto (Avanto; Siemens, Erlangen, Germany) magnet using the body and spine array coils.

1. Coronal and axial Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) images of the abdomen and pelvis were acquired during breathe hold with and without fat saturation

FOV	Variable
No. of sections	20/26*
Stacks	1/4
TR (ms)	1200
TE (ms)	86
Matrix	256 x 195
Slice thickness (mm)	4
Section gap (mm)	1
Averages	4
Echo train	256
Integrated parallel acquisition technique	Grappa factor of 2
Flip angle	50 degrees

*coronal/axial acquisition

**Grappa= generalized autocalibrating partially parallel acquisitions

MR parameters-Coronal and axial Half Fourier RARE sequence

2. 2nd dose Intravenous hyoscine butylbromide
3. Diffusion weighted imaging of abdomen (WB-DWI) x 2 b-values (ADC quantitation)
4. The pre – contrast T1 relaxation time of colon was measured by using three breath-hold coronal fat saturated 3D Fast Low Angle Shot (FLASH) images of the abdomen and pelvis with different excitation flip angles (flip angles 5°, 10°, and 35°)
5. Prior to intravenous contrast administration, three 3D FLASH baseline sets of coronal images were acquired during suspended inspiration.
6. A single dose of (0.2 mg/Kg) IV gadoterate meglumine (Dotarem; Guerbet Roissy, France) was then injected into an arm vein at 3 mL/sec, followed by a saline chaser (10 mL).
7. At injection the patient was asked to hold his/her breath for 20 seconds (during which a single 3D FLASH volume dataset was acquired), followed by 10 seconds of gentle breathing, immediately followed by another 20 seconds breath hold acquisition and 10 seconds of gentle breathing. The acquisition protocol was repeated to generate a total of 8 post contrast 3D FLASH datasets.

	*FLASH 3D (T1 calculation)	*FLASH 3D (pre-contrast)	*FLASH 3D (post-contrast)
TE (ms)	2.4	2.4	2.4
TR (ms)	5.15	5.15	5.15
FA (degrees)	5°,10°,35°	35°	35°
NEX	1	1	1
iPAT	2	2	2
FOV (mm)	500x500	500x500	500x500
STH	3	3	3
No. slices	48-60	48-60	48-60
BW (Hz)	300	300	300
Acq. Matrix	256x154	256x154	256x154
Recon. Matrix	512x512	512x512	512x512
TA (s)	17	17	17
No. Acq.	**1	3	8

MR Acquisition Parameters

*Breath held fat saturated coronal T1 weighed 3D Fast Low Angle Shot

**Single acquisition at each flip angle

TR- repetition time, TE- echo time,

FA- flip angle, NEX- number of signal

iPAT- parallel imaging factor

FOV- field of view, STH- slice thickness

BW- pixel bandwidth

TA- time for single 3D FLASH acquisition.

APPENDIX D – Patient information sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Endoscopy is a test used to examine the large bowel (colon) for polyps, tumours and inflammation. Endoscopy involves passing a tube into the large bowel in order to look around. Generally endoscopy is safe and not unduly uncomfortable but it is an expensive, time-consuming and difficult procedure and, very rarely, patients may be harmed by it. MRI scanning is a safe and less invasive way of imaging the body and produces images or pictures of the bowel without using X-rays. It may be possible to get much of the information given by endoscopy by using MRI (with a test called MR colonography). We are particularly interested to see if MR Colonography can detect inflammation in bowel (such as with Crohn's disease or ulcerative colitis). This study will compare the ability of MR colonography to detect inflammation in the bowel compared to conventional colonoscopy with the aim of in part replacing endoscopy with MRI.

Why have I been chosen?

You have been chosen because you are due to undergo a conventional endoscopy to look inside your large bowel because your doctor thinks you may have inflammation of

the bowel. We would like to see how good MR Colonography is at assessing large bowel inflammation compared to conventional endoscopy.

Do I have to take part?

It is up to you to decide whether or not to take part. You have at least 48 hours to consider participation. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. A research doctor (Dr Rehana Hafeez) may ring you before the date of the endoscopy to explain the study in more detail and answer any questions or concerns you may have. In the mean time please feel free to contact Dr Hafeez on 07877 931 401 if you would like to discuss anything before this phone call

If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your future medical care.

What is happen to me if I take part?

We will ask you to come to the hospital for an MRI scan of the large bowel around 2 hours before the time of your scheduled endoscopy. The scan will take about 30 minutes. We will ask you to lie in the MR scanner and we will insert a small needle into a vein in your arm. We will leave this needle in so it can be used during your subsequent endoscopy. During the scan we will give you two small injections through this needle (the injections themselves will not hurt). One injection (“buscopan”) relaxes the bowel (and may temporally give you a dry mouth and slightly blurred vision). The second injection (“gadolinium”) is a special MRI contrast agent which helps highlight the wall of the bowel. It is unlikely you will notice anything during this injection,

although some people get a sweet taste in their mouth. Before we start the MRI scan, a small tube will be put just inside your bottom and some gas or water introduced through this, to distend your large bowel, just like happens during endoscopy. You may feel some abdominal bloating as the gas or water is put in the large bowel, but the procedure should not be painful.

The main aim of the trial is to compare the MRI appearance of your bowel with that seen during your conventional endoscopy so we can learn what the MRI scan images mean.

What do I have to do?

You will need to follow the preparation instructions already needed for your conventional endoscopy. You will not have to do anything more because of the MRI scan. As explained above we may give you a small injection during the scan which may temporarily cause minimal blurring of your vision and affect your ability to drive for about an hour or so. If you are pregnant we will ask you not to take part in the study. After the MRI scan is complete we will escort you in your own time to the endoscopy department where you will be able to wait for your endoscopy appointment. We will ask you to fill out a short questionnaire after the MR scan and endoscopy so you can tell us how you found both tests. With your permission, we may telephone you afterwards to give us more detailed information about your experience during the scan.

What is the drug or procedure that is being tested?

MRI is an established imaging test and is increasingly used to look at the large bowel. However we are not completely sure what the abnormalities seen on MRI actually mean, and how good it is at showing the severity of inflammation. We ultimately would

like to use MRI as a reliable non invasive test to see whether the bowel is inflamed. By comparing MRI scans with endoscopy, we hope to gain important information which will be used to interpret scans in the future.

What are the alternatives for diagnosis or treatment

At the moment doctors try and assess if the large bowel is abnormal by inserting a endoscope and looking at the bowel directly.

What are known risks of the study or the side effects of any treatment received?

MRI is a safe test and importantly does not use X-rays which are theoretically harmful. There are no known adverse effects from MRI itself. However certain patients cannot have MRI (e.g. people with heart pacemakers) and we will ask you detailed questions to make sure it is safe for you to have the scan. Some people find being in the scanner a little claustrophobic. However modern scanners have a larger space to lie in and you will always be in contact with the person performing the scan via an intercom. The scan takes no more than 30 minutes and can be done in stages if you prefer. The injections we give have been used in day to day practice for a long time and are very safe. As mentioned above the buscopan injection may give you dry mouth and slightly blurred vision for a few minutes. Allergy to the gadolinium contrast is possible but very rare. Mild reactions (nausea, transient rash etc.) occur in less than 3% of patients and more serious reactions are much less common than this. The risk of causing damage to your bowel such as making a small hole by gently inflating with gas or water, is very small (less than 3 in 10,000 similar procedures i.e. 0.03%), and less than the risk of conventional endoscopy.

You are encouraged to contact Dr Hafeez on 07877 931 401 if you have any problems after the scan.

What are the possible disadvantages and risks of taking part?

Because we are not totally sure if MRI is completely safe in the early stages of pregnancy, we asked pregnant women not to take part in the study. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy.

The MRI scan will mainly look at the large bowel. However we will also obtain some imaging information about the other organs in your abdomen such as liver, kidneys etc. We may theoretically therefore detect an incidental abnormality in one of these organs which may need further investigation to clarify its nature. The vast majority of such findings are incidental to and of little importance. Your doctor will be informed of the finding via the clinical report we will provide for the MRI scan. If you have private medical insurance you are advised to check with the company before agreeing to take part in the trial.

What are the possible benefits of taking part?

By taking part in the study you will have an MRI scan which you otherwise would not have had. The scan will allow us to look at the extent of inflammation in your bowel and detect any associated complication such as abscess or fistulae (abnormal communications from the bowel). This information may be of use to your doctor, and we will provide a full clinical report for the scan so all the information is passed on. You may receive no direct benefit from taking part, but the information from this will be of use for patients in the future.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interest to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

After the study is complete we will aim to analyse the results, write them up in medical journals and hopefully change to way we interpret scans. We hope to use the information to start new trials looking at how we monitor the effect of medication given to treat colonic inflammation.

What if something goes wrong?

If you have a specific complaint against your treatment by a member of staff (doctors, nurses, etc.) you have the right to complain using the usual UCLH complaints procedure.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this,

if you wish to complain, or have any concerns of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognized from it. We will need to look at your hospital notes, blood results and past x-ray tests, but only medically qualified doctors at UCH involved in this study will do this.

With your permission, we will tell your GP that you are taking part in the trial and we will tell them the results of your MRI scan if you want them to know. The results of the MRI scan will be available to your GP and other hospital doctors looking after you by the usual hospital results system. Please tell us if you do not want your GP to be informed.

Your data

We will create a database for the trial. The data will be anonymised such that your name, hospital number date of birth and address will be fully removed and you will be given a unique trial identification number. The list of identification numbers will be held on a password protected secure computer separate from the database controlled by trial principal investigator (Dr Stuart Taylor). We will store basic information such as your age, as well as results of previous imaging/blood tests, the results of your MRI scan and pathology reports. The database will be stored on a password protected computer drive held by UCL who will collect, store, handle and process the data. Only the trial principal investigator (Dr Stuart Taylor) and nominated researchers will have access to

the data base and will be responsible for the safely and security of the data. With your permission will may use your data for future studies, although again it will be anonymised and handled as explained above. For this reason we expect to keep the database for 3 years. The study does not involve storage of any body tissue over and above your normal clinical care.

What will happen to the results of the research study?

We aim to recruit around 55 patients for the study. When we have analyzed the results we will write them up and publish them in medical journals. It will probably take about a year from completing the trial to publishing the results. Your doctor at UCH will be able to tell you about the results when they are published so you can get a copy if you wish. In the mean time you will be able to discuss your MRI scan results with your doctor at UCH. You will not be identified in any report/publication.

Who is organizing and funding the research?

The research is being funded via a research grants from the Royal College of Radiologists and the UCLH Trustees.

No doctor is being paid for conducting the research.

The costs of the MRI scan will be paid by the funding organizations.

Who has reviewed the study?

The study has been reviewed by University College Hospital Ethics Committee A

Contact for Further Information

Thank you very much for considering taking part in the study. If you agree to take part we will provide you with copies of this information sheet and the consent form we will ask you to sign.

APPENDIX E- Patient Questionnaire

We would like to thank you for taking part in the study comparing MRI colonography and colonoscopy. For each item below please place a cross in the box which you feel best reflects your experience of MRI/CC

Frightened	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not frightened
Worried	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not worried
Agitated	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Calm
Worried what find	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not worried
As expected	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not as expected
Understood	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not understand
Puzzled	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not puzzled
Confused	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not confused

Dissatisfied ■ ■ ■ ■ ■ ■ ■ ■ Satisfied
 Staff not interested ■ ■ ■ ■ ■ ■ ■ ■ Staff interested
 Displeased ■ ■ ■ ■ ■ ■ ■ ■ Pleased
 Staff cool ■ ■ ■ ■ ■ ■ ■ ■ Staff warm
 Staff uninformative ■ ■ ■ ■ ■ ■ ■ ■ Staff informative
 Undignified ■ ■ ■ ■ ■ ■ ■ ■ Dignified
 Uninterested ■ ■ ■ ■ ■ ■ ■ ■ Interested
 Not confident ■ ■ ■ ■ ■ ■ ■ ■ Confident in Staff

Weary after ■ ■ ■ ■ ■ ■ ■ ■ Not weary
 Painful ■ ■ ■ ■ ■ ■ ■ ■ Not painful
 Uncomfortable ■ ■ ■ ■ ■ ■ ■ ■ Not Uncomfortable
 Bad experience ■ ■ ■ ■ ■ ■ ■ ■ Good experience
 In control ■ ■ ■ ■ ■ ■ ■ ■ Not in control
 Soreness ■ ■ ■ ■ ■ ■ ■ ■ No soreness
 Afraid making a fool of myself ■ ■ ■ ■ ■ ■ ■ ■ Not afraid
 Relieved when over ■ ■ ■ ■ ■ ■ ■ ■ Not relieved
 Preferred to be less awake ■ ■ ■ ■ ■ ■ ■ ■ Preferred to be more awake

APPENDIX F- Follow up questionnaire

We would like to thank you again for taking part in our study comparing a MR colonography scan with endoscopy for looking at the large bowel. You have now had some time to recover from both tests. We would like to see how you think you tolerated the two tests and if you found one more acceptable than the other. Please answer the following questions:

- I felt I tolerated the MRI scan (circle one response)

Well Fairly well Poorly Very Poorly

If you ringed poorly or very poorly please give the reasons:

- What was the worst part of the MRI scan (circle one response)

Injections having gas put lying flat claustrophobia

In the bowel

Other (please state) -----

- I felt I tolerated the colonoscopy (circle one response)

Well Fairly well Poorly Very Poorly

If you ringed poorly or very poorly please give the reasons:

- What was the worst part of the colonoscopy (circle one response)

Injections moving the having gas other (please state)

Colonoscope put in the _____

In the bowel bowel _____

How long did it take for you feel back to normal after the MRI scan (circle one response)?

Less than 1 hour 1-3 hours 3- 6 hours More than 6 hours

Please state how long _____

- How long did it take for you feel back to normal after the colonoscopy?

Less than 1 hour 1-3 hours 3- 6 hours More than 6 hours

Please state how long _____

If your recovery was more than 1 hour, please give the main reasons why you felt you were not back to normal _____

- Would you have the endoscopy again?

Yes No Maybe

- Would you have the MRI again?

Yes No Maybe

- If you had to have just one of the tests again, which one would it be?

MRI scan Endoscopy Don't mind

- Baring in mind all that you personally know about the risks and benefits for both tests, which one do you feel is the most acceptable?

MRI scan Endoscopy About the same

- If you found one of the tests more acceptable than the other, please write of few words below to give your reasons.

Many thanks for your time. Please return this questionnaire in the enclosed SAE

PUBLICATIONS ARISING FROM THIS THESIS

ORIGINAL ARTICLES

Hafeez R, Greenhalgh R, Rajan R, Bloom J, McCartney S, Halligan S, Taylor S.

Use of small bowel imaging for the diagnosis and staging of Crohn's disease--a survey of current UK practice

Br J Radiol 2011; 84(1002): 508-517

Hafeez R, Punwani S, Boulos P, Bloom S, McCartney S, Halligan S, Taylor S.

Diagnostic and therapeutic impact of MR enterography in Crohn's disease

Clin Radiol 2011; 66 (12): 1148-1158

Hafeez R, Punwani S, Pendse D, Boulos P, Bloom S, Halligan S, Taylor S.

Derivation of a T2-weighted MRI total colonic inflammation score (TCIS) for assessment of patients with severe acute inflammatory colitis-a preliminary study

Eur Radiol 2011. 21(2): 366-377.

Hafeez R, Wagner C. V, Smith S, Boulos P, Halligan S, Bloom S, Taylor S.

Patient experiences of MR colonography and colonoscopy: a qualitative study.

Br J Radiol 2011 Oct 18 [Epub ahead of print]

Punwani S, Hafeez R, Bainbridge A, Boulos P, Halligan S, Bloom S, Taylor S.

Quantitative Magnetic Resonance Imaging of colonic mural enhancement: Segmental differences exist in endoscopically proven normal colon

Br J Radiol 2011 [in press]

ABSTRACTS

Hafeez R, Punwani S, Pendsé D, Bainbridge A, Boulos P, Halligan S, Taylor SA.

Validation of T2-weighted MRI derived colonic inflammation score for patients with acute colitis

ESGAR 2009 Book of Abstract/volume 19/ supplement 2/ SS 3.03

Hafeez R, Punwani S, Pendsé D, Bainbridge A, Boulos P, Halligan S, Taylor SA.

Correlation of colonic mural apparent diffusion coefficient and clinical/biochemical markers of inflammation in acute colitis

ESGAR 2009 Book of Abstract/volume 19/ supplement 2/ SS 3.04

Hafeez R, Boulos P, Bloom S Punwani S, Taylor SA.

Diagnostic and therapeutic impact of MR enterography in Crohn's disease: a prospective non-randomized study

ESGAR 2009 Book of Abstract/volume 19/ supplement 2/ SS 15.04

Hafeez R, Punwani S, Boulos P, Halligan S, Taylor SA.

Diagnostic and therapeutic impact of MR enterography in Crohn's disease: a prospective non randomized study

ECR 2010 Book of Abstracts/ Volume 1/ Supplement 1/ March 2010

Hafeez R, Punwani S, Boulos P, Halligan S, Taylor SA

To investigate the utility of T2 relaxation time measurement as a potential biomarker of inflammation in acute colitis.

ECR 2010 Book of Abstracts/ Volume 1/ Supplement 1/ March 2010

Hafeez R, Taylor SA, Punwani S, Steward M, Bloom S, Boulos P, Pendse D, Halligan S.

Utility of an MRI derived T2 weighted colonic inflammation score as an independent prognostic marker in acute colitis

ESGAR 2010 Book of Abstracts / Volume 20/ Supplement 1/ SS 7.10

Hafeez R, Taylor SA, Punwani S, Steward M, Boulos P, Halligan S.

Intersegment variation in MRI –derived perfusion in normal colon

ECR 2011 Book of Abstracts/ Volume 2/ Supplement 1/ March 2011

Taylor SA, Punwani S, Hafeez R, Bainbridge A, Boulos P, Halligan S.

Magnetic resonance imaging contrast-enhance mural perfusion kinetic: segmental differences exist in endoscopically proven normal colon

ESGAR 2011 Book of Abstracts/ Volume 2/ Supplement 2/ SS 15.01

Hafeez R, Punwani S, Bainbridge A, Boulos P, Halligan S, Bloom S, Taylor SA.

Quantitative Magnetic Resonance Imaging of colonic mural enhancement: segmental differences exist in endoscopically proven normal colon

Clinical Radiology 2011; 66 (Suppl 1): S9

PRESENTATIONS AND POSTERS

June 2009: **European Society of Gastrointestinal and Abdominal Radiology/**

ESGAR Annual meeting

Valencia Spain

- Validation of T2-weighted MRI derived colonic inflammation score for patients with acute colitis
- Correlation of colonic mural apparent diffusion coefficient and clinical/biochemical markers of inflammation in acute colitis
- Diagnostic and therapeutic impact of MR enterography in Crohn's disease: a prospective non-randomized study

March 2010: **European Congress of Radiology/ ECR Annual meeting**

Vienna, Austria

- Can colonic mural apparent diffusion coefficient act as an imaging biomarker of inflammation in acute colitis?

DOI: 10.1594/ecr2010/C-1504

- Derivation of T2- weighted MRI based total colonic inflammatory scoring for assessing therapeutic response in colitis

DOI: 10.1594/ecr2010/C-1505

June 2010: **European Society of Gastrointestinal and Abdominal Radiology/**

ESGAR Annual meeting

Dresden, Germany

Use of Small bowel Imaging investigation for the diagnosis and staging of Crohn's disease – a survey of current UK practice

EPOS SE- 045

March 2011: **European Congress of Radiology/ ECR Annual meeting**

Vienna, Austria

Intersegment variation in MRI –derived perfusion in normal colon

May 2011: **European Society of Gastrointestinal and Abdominal Radiology/**

ESGAR Annual meeting

Venice, Italy

Patient experience of MR Colonography and colonoscopy: a qualitative study

DOI: 10.5444/esgar2011/SE-005

Sep 2011: **Royal College of Radiology annual scientific meeting**

London, UK

Quantitative Magnetic Resonance Imaging of colonic mural enhancement: segmental differences exist in endoscopically proven normal colon.